Asymmetric Synthesis of 2-Substituted Hexahydroquinolin-4-ones Using a Pd-Catalyzed Asymmetric Allylic Amination and Intramolecular Mannich Reaction: Catalytic Asymmetric Synthesis of 2-*epi*-*cis*-195A

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Abstract: A novel method of the enantioselective synthesis of 2-substituted hexahydroquinolin-4-ones is described. The method relies on a Pd-catalyzed asymmetric allylic amination using a chiral diaminophosphine oxide (DIAPHOX) preligand and diastereoselective intramolecular Mannich reaction. The developed synthetic method could be applied to the catalytic asymmetric synthesis of (+)-2-*epi*-*cis*-195A.

Key word: asymmetric allylic amination, asymmetric synthesis, chiral diaminophosphine oxide, decahydroquinoline alkaloid, intramolecular Mannich reaction, palladium

Decahydroquinoline ring systems are ubiquitous structural motifs in various biologically active compounds. Since the first isolation of a representative decahydroquinoline alkaloid *cis*-195A (pumiliotoxin C) from skin extracts of the Panamanian frog *dendrobatus pumilio*,[1] approximately 50 decahydroquinoline alkaloids have been isolated from dendrobatide and mantelline frogs,[2] bufonid toads,[3] tunicates,[4] marine flatworms,[5] and myrmicine ants.[6] Decahydroquinoline alkaloids generally possess a *cis*- or *trans*-fused azabicyclic structure with a side-chain substituent at both the C-2 and C-5 positions (Figure 1). These alkaloids, however, cannot be obtained from their natural sources in sufficient quantities for NMR analysis and X-ray crystal structure analysis. Therefore, the structure and stereochemistry of many decahydroquinoline alkaloids have been only tentatively assigned based on MS and IR spectra.[7] Some decahydroquinoline alkaloids exhibit neurological activity as reversible antagonists of the nicotinic acetylcholine receptor channel.[8] An inhibitory effect against sodium and potassium transport has been also reported.[9] These profiles make this class of compounds an attractive target in the field of pharmaceutical chemistry.

Due to the structural diversity and interesting biological activities of decahydroquinoline alkaloids, extensive efforts have been directed towards the synthesis of these alkaloids and their structurally related heterocyclic compounds. Total synthesis of *cis*-195A has been most intensively studied since the 1980s. In addition to racemate syntheses,[10] several enantioselective total syntheses have been achieved using chiral auxiliaries[11] or a catalytic asymmetric synthesis.[12] Natural or unnatural epimers of *cis*-195A such as *trans*-195A,[13a,b] 4a-*epi*-Pmiliotoxin C,[13c] 2-*epi*-*cis*-195A,[11a,d,13d] are also attractive targets for synthetic organic chemists (Figure 1). Asymmetric total syntheses of *trans*-219A[14] and gephyrotoxin[15] have been accomplished. General strategies for constructing the 2,5-disubstituted decahydroquinoline skeleton bearing four asymmetric carbon centers in an enantioselective manner would allow access to various decahydroquinoline alkaloids for unequivocal determination of their ambiguous molecular structure. Furthermore, new synthetic entries to functionalized hydroquinolines can be applied to the synthesis of other natural products with a 1-azabicyclo[3.3.0] skeleton and pharmacologically interesting heterocycles.[16,17]

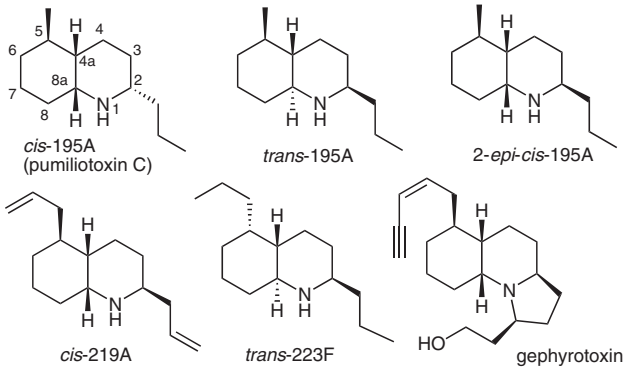

Figure 1 Representative decahydroquinoline alkaloids

An efficient method of introducing an amine unit to six-membered-ring carbon skeletons in an enantioselective manner can be a powerful tool for the asymmetric synthesis of decahydroquinoline alkaloids. Since the first report in 2004,[18] we have intensively studied transition-metal-catalyzed asymmetric allylic substitution using aspartic acid-derived P-chiral *dia*mino*ph*osphine *ox*ides: DIAPHOXs.[19] These pentavalent phosphorus compounds, preligands, are activated in situ by *N*,*O*-bis(trimethylsilyl)acetamide (BSA)-induced tautomerization to afford trivalent phosphorus compounds that function as the actual ligands. The DIAPHOX preligands are effective for Pd-catalyzed asymmetric allylic substitution of cyclic allylic carbonates with various amine nucleophiles.[20] As shown in Scheme 1, asymmetric allylic amination of an ester-

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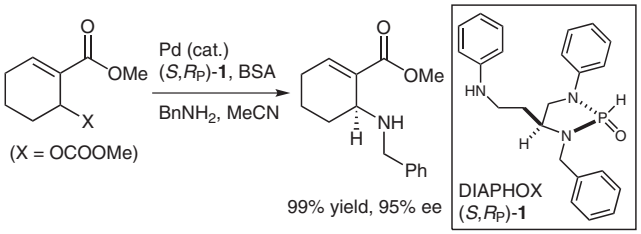
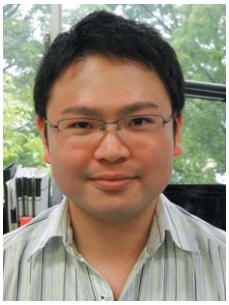
conjugated cyclohexenyl carbonate using benzylamine as a nucleophile gave the corresponding chiral amine in excellent yield with high enantiomeric purity. The suitably functionalized structure of the reaction product led us to investigate catalytic asymmetric synthesis of 2,5-disubstituted decahydroquinolines. Herein, we describe a new method of synthesizing 2-substituted hexahydroquinolin-4-ones as optically active compounds through a Pd-catalyzed asymmetric allylic amination and diastereoselective intramolecular Mannich reaction sequence, which can be successfully applied to the catalytic asymmetric synthesis of (+)-2-*epi*-*cis*-195A.



Scheme 1 Pd-catalyzed asymmetric allylic amination using chiral diaminophosphine oxide preligand (*S*,R_P)-**1**

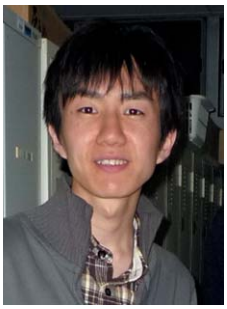
The synthetic plan for enantioselective synthesis of 2,5-disubstituted decahydroquinolines is shown in Scheme 2. Retrosynthetically, 2,5-disubstituted azabicyclic ketone **2**

Biographical Sketches



Kazumi Kakugawa was born in Chiba, Japan, in 1984. He received his B.S. (2008) and M.S. (2010) degrees from Chiba University under the direction of Prof. Yasumasa Hamada. He is currently a Ph.D. course student in Prof. Hamada's group. His current research interests include the development of novel methods for the synthesis of heterocyclic compounds.

Tetsuhiro Nemoto was born in Chiba, Japan, in 1976. He received his B.S. (1999), M.S. (2001), and Ph.D. (2005) degrees from the University of Tokyo under the direction of Prof. Masakatsu Shibasaki. In 2002, he also worked as a JSPS Research Fellow. In 2003, he started his academic career as an assistant professor in Prof. Yasumasa Hamada's group at Chiba University. He has received the Banyu Award in Synthetic Organic Chemistry (2004), Inoue Research Award for Young Scientists (2005), Daiichi-Sankyo Award in Synthetic Organic Chemistry (2007), the Pharmaceutical Society of Japan Award for Young Scientists (2008), and the Thieme Chemistry Journal Award (2011). His current research interests include asymmetric catalysis and synthetic organic chemistry.



Yuta Kohno was born in Chiba, Japan, in 1985. He received his B.S. degree (2010) from Chiba University under the direction of Prof. Yasumasa Hamada. After spending one year as a graduate student in Prof. Hamada's group, he started working in the analytical department of Tokyo metropolitan.

Yasumasa Hamada is Professor of Pharmaceutical Chemistry at Chiba University. He was born in Hokkaido in 1949 and received his B.S. degree (1973) from Toyama University and M.S. degree (1975) from the University of Tokyo. In 1977, he joined Nagoya City University as an assistant professor. After obtaining his Ph.D. in 1982 and one year postdoctoral work with Prof. E. J. Corey at Harvard University in 1985, he was promoted to associate professor at Nagoya City University in 1988. In 1995, he moved to Chiba University to take up his present position. He received the Pharmaceutical Society of Japan Award for Young Scientists in 1990 and the Pharmaceutical Society of Japan Award in 2011. His research interests include the development of new methods and reagents for use in organic synthesis and total synthesis of biologically active natural products.

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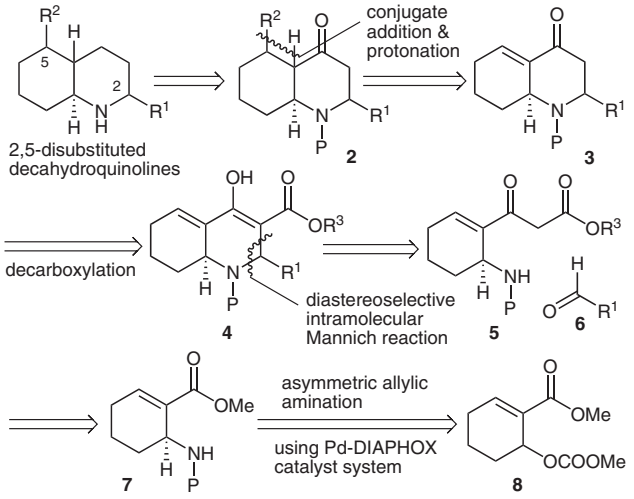
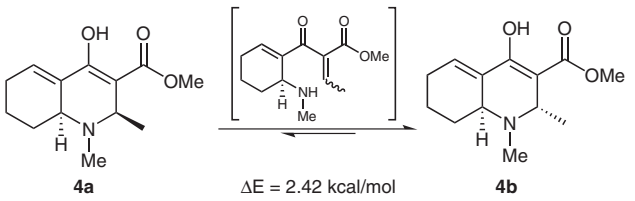
would be a reasonable precursor of the target decahydroquinolines, which, in turn, would be obtained from **3** via diastereoselective conjugate addition and protonation. There is a β-amino ketone motif in the α,β-unsaturated ketone **3**. Therefore, we envisioned that an intramolecular Mannich reaction using δ-amino β-keto ester **5** and aldehyde **6**, followed by a decarboxylation reaction of **4**, would be applicable to construct the azabicyclic core in **3**. Finally, compound **7**, a promising precursor of **5**, can be prepared via asymmetric allylic amination of **8** with a flexibly deprotectable amine such as 4-methoxybenzylamine using the Pd-DIAPHOX catalyst system.



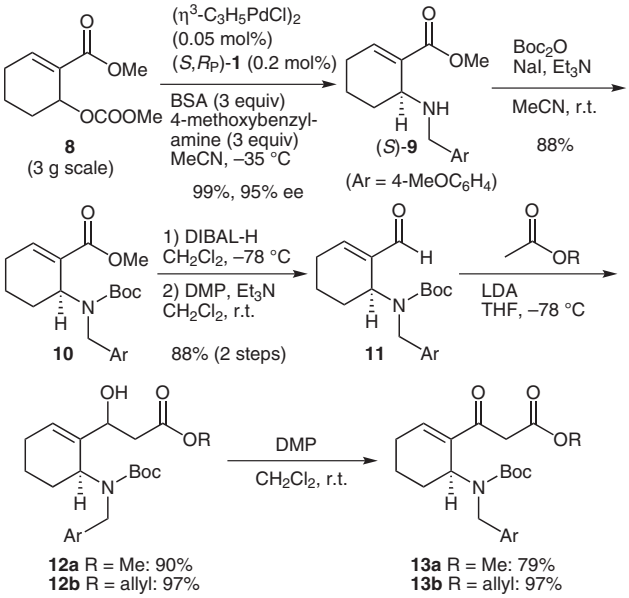
Scheme 2 Retrosynthetic plan for 2,5-disubstituted decahydroquinolines

Considering the structure of compound **4**, the stereochemistry at the C-2 position is expected to epimerize through the retro-aza-Michael reaction (Scheme 3). The molecular energy calculation (M06-2X/6-31G**) of model compounds **4a** and **4b** revealed that **4b** is 2.42 kcal/mol more stable than **4a**, indicating that thermodynamically stable **4b**-type adducts would be obtained as the major product.[21]



Scheme 3 Thermodynamic stability of azabicyclic adducts

Our synthesis began with the preparation of optically active δ-amino β-keto esters through an asymmetric allylic amination using the Pd-DIAPHOX catalyst system (Scheme 4). Using 0.05 mol% of $[\eta^3\text{-}C_3H_5PdCl]_2$, 0.2 mol% of ($S$,$R_P$)-**1**, and BSA, asymmetric allylic amination of **8** with 4-methoxybenzylamine proceeded at –35 °C, providing the corresponding product (S)-**9**[20b] in 99% yield with 95% ee. After protection of the secondary amine with a *tert*-butoxycarbonyl (Boc) group (88% yield), α,β-unsaturated ester **10** was converted into the corresponding α,β-unsaturated aldehyde **11** by a two-step process involving diisobutylaluminum hydride (DIBAL-H) reduction, followed by oxidation with Dess–Martin periodinane (DMP) (88% yield, 2 steps). Subsequent aldol reaction of **11** with lithium ester enolates proceeded smoothly at –78 °C, affording the corresponding adducts **12a** and **12b** in over 90% yield. Finally, Dess–Martin oxidation of the alcohol provided δ-amino β-keto esters **13a** and **13b** in 79% and 97% yield, respectively.



Scheme 4 Preparation of δ-amino β-keto esters using Pd-catalyzed asymmetric allylic amination

With the substrates in hand, the construction of the azabicyclic skeleton through the diastereoselective intramolecular Mannich reaction (Table 1) was next examined. After removal of the Boc group of **13a** under acidic conditions, the resulting amine trifluoroacetate salt was reacted with *n*-butyraldehyde in the presence of sodium bicarbonate and 3 Å molecular sieves (MS) at room temperature. After 48 hours, the desired azabicyclic compound **15aa** was obtained in 79% yield with a 98:2 diastereomeric ratio (Table 1, entry 1). The same reaction using allyl ester-type substrate **13b** also gave **15ba** in 98% yield as a nearly diastereomerically pure compound (entry 2). On the other hand, when this reaction was quenched after four hours, a diastereomeric product mixture was obtained in 52% yield with a ca. 2:1 ratio, clearly indicating that the product ratio of this cyclization process was thermodynamically controlled (entry 3). Intramolecular Mannich reactions with some other aldehydes were also examined using **13b** under the same reaction conditions. Primary aldehydes, an α-branched primary aldehyde, an aromatic aldehyde, and an α,β-unsaturated aldehyde could be utilized for this process, giving the corresponding products in moderate to high yield with excellent diastereoselectivity (entries 4–9). NOE experiments revealed that the stereochemistry of

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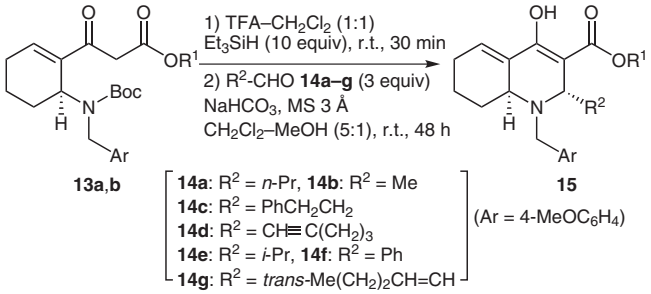
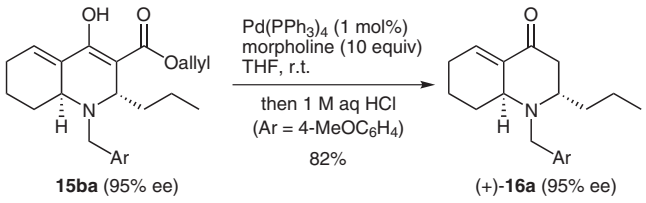
15bb was 2*S*,8a*S*, consistent with the computational prediction shown in Scheme 3.[22]

Table 1 Diastereoselective Intramolecular Mannich Reaction



Entry	Substrate	Aldehyde	Product	Yield (%)[a]	dr
1	**13a**	**14a**	**15aa**	79	98:2
2	**13b**	**14a**	**15ba**	98 (87)[b]	>99:1
3[c]	**13b**	**14a**	**15ba**	52	67:33
4	**13b**	**14b**	**15bb**	50	>99:1
5	**13b**	**14c**	**15bc**	87	>99:1
6	**13b**	**14d**	**15bd**	66	>99:1
7	**13b**	**14e**	**15be**	74	94:6
8	**13b**	**14f**	**15bf**	57	98:2
9	**13b**	**14g**	**15bg**	47	97:3

[a] Yield of diastereomeric mixture.
[b] Isolated yield for the reaction on a 15.2 g scale.
[c] Reaction was quenched in 4 h.

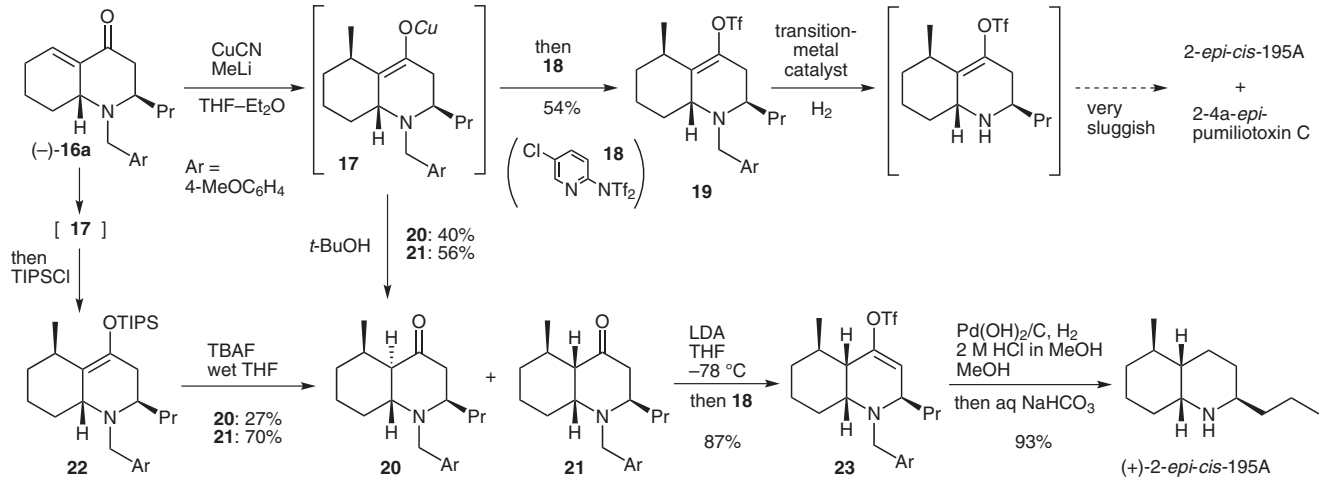


Scheme 5 Decarboxylation of **15ba**

We next performed decarboxylation of the reaction products. Allyl esters are easily transformed to the corresponding carboxylate in the presence of Pd catalyst and amine nucleophiles. In practice, a deallylation reaction of **15ba** (95% ee)[23] proceeded smoothly using 1 mol% of $Pd(PPh_3)_4$ and 10 equivalents of morpholine in THF at room temperature. After the starting material was consumed, 1 M aqueous HCl was added subsequently to the reaction mixture to give 2-propylhexahydroquinoline-4-one (+)-**16a** (95% ee)[23] in 82% yield (Scheme 5).

Having established the synthetic route to enantiomerically enriched 2-propylhexahydroquinolin-4-one **16a**, our attention was focused next on the enantioselective synthesis of 2-*epi*-*cis*-195A (Scheme 6). As shown in Scheme 1, the stereochemistry at the C-8a position of *cis*-195A is *R*. Therefore, (2*R*,8a*R*)-(–)-**16a** with 95% ee was first prepared using the developed method, where DIAPHOX preligand (R,S_P)-**1** derived from (*R*)-D-aspartic acid was utilized in the Pd-catalyzed asymmetric allylic amination step. Conjugate addition of an organocopper reagent prepared from CuCN and methyllithium (CuCN/MeLi = 1:2) to (–)-**16a**, followed by entrapment of the copper enolate **17** with *N*-(5-chloro-2-pyridyl)bis(trifluoromethansulfonimide) (**18**),[24] afforded triflate **19** in 54% yield as a single diastereomer. When the copper enolate **17** was quenched with *tert*-butanol as a proton source, diastereomeric mixtures **20** and **21** were obtained in 40% and 56%, respectively. Relative configurations of **20** and **21**, determined by NOE experiments,[22] revealed that the conjugate addition predominantly occurred from the stereoelectronically preferred β-axial direction of (–)-**16a** (*Re*-face attack).[22,25]

Compound **19** can be directly transformed to 2-*epi*-*cis*-195A by treating with hydrogen in the presence of a transition-metal catalyst through a series of reactions involving the reductive removal of triflate, diastereoselective hydrogenation, and the removal of a 4-methoxybenzyl group. The reductive removal of triflate was, however, very sluggish under several reaction conditions [Pd/C, H_2, MeOH; $Pd(OH)_2$/C, H_2, MeOH–2 M HCl–MeOH; $Pd(OH)_2$/C, H_2 (100 atm), MeOH–2 M HCl–MeOH].



Scheme 6 Asymmetric synthesis of (+)-2-*epi*-*cis*-195A

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Therefore, the synthetic route was changed to that using compound **21** as the key intermediate. Although the reaction was quenched with various proton donors to improve the isolate yield of **21** from **17**, all trials gave less satisfactory results.[22] On the other hand, the diastereoselective protonation proceeded with improved efficiency using the corresponding enol triisopropylsilyl (TIPS) ether **22**. After conversion of **17** into compound **22** by trapping with TIPSCl, the copper species was removed from the reaction mixture by washing with ammonia solution. The obtained crude **22** was allowed to react with tetrabutylammonium fluoride (TBAF) in THF at room temperature, affording compound **21** in 70% yield, accompanied by the formation of **20** in 27% yield. Compound **21** was then converted into the corresponding enol triflate **23** by treatment with lithium diisopropylamide (LDA), followed by the addition of **18** (87% yield). Finally, compound **23** was reacted in the presence of Pearlman's catalyst under a hydrogen atmosphere, providing (+)-2-*epi*-*cis*-195A in 93% yield {$[\alpha]_D^{22}$ +18.1 (*c* 0.25, MeOH)}. The NMR data were identical to the data previously reported in the literature for *ent*-2-*epi*-*cis*-195A: $[\alpha]_D^{22}$ –22.2 (*c* 0.6, MeOH).[11d,13d]

In conclusion, we have developed a novel method to synthesize 2-substituted hexahydroquinolin-4-one derivatives through asymmetric allylic amination using the Pd-DIAPHOX catalyst system and diastereoselective intramolecular Mannich reaction sequence. The present method was successfully applied to enantioselective synthesis of (+)-2-*epi*-*cis*-195A in combination with a diastereoselective conjugate addition of an organocopper reagent (33% overall yield in 12 steps from compound **8**). The divergent synthetic route provides access to natural products with the same stereochemical arrangement, such as *cis*-219A and gephyrotoxin. Further studies on the application of the developed method to catalytic asymmetric synthesis of other natural products are in progress.

IR spectra were recorded on a JASCO FT/IR 230 Fourier transform IR spectrophotometer, equipped with ATR (Smiths Detection, DuraSample IR II). NMR spectra were recorded on a JEOL ecp 400 spectrometer, operating at 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR. Optical rotations were measured on a JASCO P-1020 polarimeter. ESI mass spectra were measured on JEOL AccuTOF LC-plus JMS-T100LP. The enantiomeric excesses were determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, PU-980; detector, UV-970, measured at 254 nm. Reactions were carried out in anhydrous solvents. Other reagents were purified by the usual methods.

6-Methoxycarbonyloxycyclohex-1-enecarboxylic acid methyl ester (**8**) was prepared according to the literature procedure.[20b,26]

(6*S*)-6-(4-Methoxybenzylamino)cyclohex-1-enecarboxylic Acid Methyl Ester (9)[20b]

To a solution of $[\eta^3$-$C_3H_5PdCl]_2$ (2.7 mg, 0.0072 mmol), (*S*,R_P)-**1** (11.3 mg, 0.028 mmol), and **8** (3.06 g, 14.4 mmol) in MeCN (72 mL) at r.t. was added BSA (10.7 mL, 43.2 mmol). After stirring the solution at r.t. for 10 min, and then at –40 °C for 30 min, 4-methoxybenzylamine (5.6 mL, 43.2 mmol) was added to the reaction mixture over 30 min. After stirring at –35 °C for 48 h, the resulting mixture was allowed to warm to r.t., and the solvent was removed under reduced pressure. The obtained crude residue was purified by flash column chromatography to give (*S*)-**9** (3.94 g, 14.3 mmol, 99%) as a pale yellow oil; $[\alpha]_D^{23}$ –60.9 (*c* 1.40, $CHCl_3$); 95% ee. The enantiomeric excess was determined by chiral HPLC analysis after converting into the corresponding *tert*-butyl carbamate **10** {DAICEL CHIRALPAK AD-H, hexane–propan-2-ol, 97:3, flow rate: 0.5 mL/min, t_R 32.1 min [(*R*)-isomer] and 38.3 min [(*S*)-isomer], detection at 254 nm}.

(6*S*)-6-[*tert*-Butoxycarbonyl-(4-methoxybenzyl)amino]cyclohex-1-enecarboxylic Acid Methyl Ester (10)

To a solution of **9** (180.2 mg, 0.654 mmol), Et_3N (0.28 mL, 2.00 mmol), and NaI (98.1 mg, 0.654 mmol) in MeCN (3.3 mL) at 0 °C was added Boc_2O (214.3 mg, 0.981 mmol), and the reaction mixture was stirred at r.t. After 12 h, the reaction was quenched with H_2O (3.3 mL), and the resulting mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried (Na_2SO_4). After concentration in vacuo, the obtained residue was purified by flash column chromatography to give **10** (215.5 mg, 0.573 mmol, 88%) as a pale yellow oil; $[\alpha]_D^{23}$ –37.6 (*c* 3.10, $CHCl_3$); 95% ee.

IR (ATR): 2946, 1716, 1684, 1511, 1241, 1162, 1035, 817, 761 cm^{-1}.

^{1}H NMR ($CDCl_3$, 55 °C): δ = 1.41 (s, 9 H), 1.40–1.90 (m, 4 H), 2.10–2.20 (m, 2 H), 3.64 (s, 3 H), 3.50–3.90 (m, 2 H), 3.79 (s, 3 H), 4.23 (d, *J* = 14.4 Hz, 1 H), 6.75–6.85 (m, 2 H), 6.95–7.25 (m, 3 H).

^{13}C NMR ($CDCl_3$, 55 °C): δ = 19.9, 25.5, 28.3 (3 C), 28.8, 48.5, 51.3, 51.7, 55.2, 79.5, 113.6 (2 C), 128.2 (2 C), 132.0, 141.8, 143.2, 155.6, 158.5, 166.9.

ESI-HRMS: *m*/*z* calcd for $C_{21}H_{29}NO_5$ + Na (M + Na^+): 398.1943; found: 398.1935.

(1*S*)-(2-Formylcyclohex-2-enyl)(4-methoxybenzyl)carbamic Acid *tert*-Butyl Ester (11)

To a solution of **10** (1.20 g, 3.20 mmol) in CH_2Cl_2 (32 mL) at –78 °C was added DIBAL-H (9.60 mL, 1.0 M in *n*-hexane, 9.60 mmol), and the reaction mixture was stirred at the same temperature. After 30 min, the reaction was quenched by the addition of MeOH (6 mL) and H_2O (32 mL), and the resulting mixture was extracted CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried ($MgSO_4$). After concentration in vacuo, the obtained residue was purified by flash column chromatography to give the corresponding alcohol (1.02 g, 2.95 mmol, 92%) as a colorless oil; $[\alpha]_D^{27}$ –68.2 (*c* 1.47, $CHCl_3$, 95% ee).

Intermediate Alcohol

IR (ATR): 2934, 1668, 1612, 1512, 1405, 1365, 1244, 1160, 1035, 976, 734, 701 cm^{-1}.

^{1}H NMR ($CDCl_3$, 55 °C): δ = 1.42 (s, 9 H), 1.35–1.85 (m, 4 H), 1.94–2.05 (m, 2 H), 2.71 (br s, 1 H), 3.78 (s, 3 H), 3.72–3.85 (m, 2 H), 3.93 (d, *J* = 14.2 Hz, 1 H), 3.90–4.10 (m, 1 H), 4.46 (d, *J* = 14.2 Hz, 1 H), 5.85–5.95 (m, 1 H), 6.77–6.90 (m, 2 H), 7.09–7.21 (m, 2 H).

^{13}C NMR ($CDCl_3$, 55 °C): δ = 21.6, 24.8, 28.1, 28.3 (3 C), 47.6, 52.9, 55.2, 64.6, 80.2, 113.8 (2 C), 127.9, 128.9, 131.8 (2 C), 137.8, 156.9, 158.6.

ESI-HRMS: *m*/*z* calcd for $C_{20}H_{29}NO_4$ + Na (M + Na^+): 370.1994; found: 370.2008.

To a solution of the obtained alcohol (147.7 mg. 0.425 mmol) and Et_3N (0.24 mL, 1.70 mmol) in CH_2Cl_2 (4.3 mL) was added Dess–Martin periodinane (360.6 mg, 0.85 mmol), and the resulting mixture was stirred for 4 h at r.t. The reaction was quenched with aq $Na_2S_2O_3$ (10 mL), and then Et_2O (4.3 mL) was added to the reaction mixture. After stirring for 1 h, the resulting mixture was extracted

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with EtOAc (10 mL), and the combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4). After concentration in vacuo, the obtained residue was purified by flash chromatography to give **11** (140.3 mg, 0.406 mmol, 96%) as a yellow oil; $[\alpha]_D^{27}$ –13.7 (*c* 4.40, $CHCl_3$); 95% ee.

11

IR (ATR): 2935, 1683, 1511, 1455, 1402, 1364, 1300, 1243, 1163, 1118, 1034 cm^{-1}.

^1H NMR ($CDCl_3$, 55 °C): δ = 1.43 (s, 9 H), 1.40–1.60 (m, 1 H), 1.65–1.90 (m, 3 H), 2.25–2.35 (m, 2 H), 3.79 (s, 3 H), 4.25 (d, *J* = 15.2 Hz, 1 H), 4.20–4.80 (m, 2 H), 6.75–6.90 (m, 3 H), 7.10–7.20 (m, 2 H), 9.36 (s, 1 H).

^{13}C NMR ($CDCl_3$, 55 °C): δ = 20.5, 26.1, 28.1, 28.4 (3 C), 49.8, 51.5, 55.1, 79.6, 113.6 (2 C), 128.6 (2 C), 131.7, 141.4, 155.4, 158.6, 175.6, 192.0.

ESI-HRMS: *m*/*z* calcd for $C_{20}H_{27}NO_4$ + Na (M + Na^+): 368.1838; found: 368.1819.

3-{(6*S*)-6-[*tert*-Butoxycarbonyl(4-methoxybenzyl)amino]cyclohex-1-enyl}-3-hydroxypropionic Acid Allyl Ester (12b)

To a solution of *i*-Pr_2NH (3.5 mL, 25.0 mmol) in THF (54 mL) at –78 °C was added *n*-BuLi (16.2 mL, 1.56 M in *n*-hexane, 25.3 mmol), and the reaction mixture was stirred at the same temperature. After 30 min, allyl acetate (2.7 mL, 25.0 mmol) was added to the solution, and the resulting mixture was stirred for additional 30 min at the same temperature. Then, a THF solution of **11** (2.91 g, 8.44 mmol in 30 mL of THF) was added to the mixture, which was kept stirring at –78 °C. After 12 h, the mixture was quenched with aq NH_4Cl (30 mL), and the resulting mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL) and dried (Na_2SO_4). After concentration in vacuo, the obtained residue was purified by flash column chromatography to give **12b** (3.65 g, 8.19 mmol, 97%) as a mixture of diastereomers (yellow oil); $[\alpha]_D^{23}$ +4.3 (*c* 3.85, $CHCl_3$); 95% ee.

IR (ATR): 2933, 1735, 1683, 1512, 1455, 1404, 1365, 1274, 1244, 1158, 1118, 1033, 981 cm^{-1}.

^1H NMR ($CDCl_3$, 55 °C): δ (major diastereomer) = 1.40 (s, 9 H), 1.20–1.50 (m, 1 H), 1.50–1.70 (m, 2 H), 1.75–1.85 (m, 1 H), 1.95–2.05 (m, 2 H), 2.40 (br s, 1 H), 2.60–3.00 (m, 2 H), 3.78 (s, 3 H), 4.04 (d, *J* = 15.6 Hz, 1 H), 4.27–4.37 (m, 1 H), 4.49 (d, *J* = 15.6 Hz, 1 H), 4.50–4.65 (m, 2 H), 4.65–4.80 (m, 1 H), 5.22 (dd, *J* = 1.2, 10.4 Hz, 1 H), 5.31 (dd, *J* = 1.2, 17.2 Hz, 1 H), 5.80–6.00 (m, 1 H), 6.05–6.16 (m, 1 H), 6.77–6.88 (m, 2 H), 7.10–7.20 (m, 2 H).

^{13}C NMR ($CDCl_3$, 55 °C): δ (major diastereomer) = 21.2, 24.8, 28.4 (3 C), 28.8, 41.3, 47.5, 53.2, 55.3, 65.2, 67.4, 80.2, 113.8 (2 C), 118.3, 126.9, 127.9, 131.9, 132.1 (2 C), 138.6, 156.2, 158.6, 172.2.

ESI-HRMS: *m*/*z* calcd for $C_{25}H_{35}NO_6$ + Na (M + Na^+): 468.2362; found: 468.2341.

3-{(6*S*)-6-[*tert*-Butoxycarbonyl(4-methoxybenzyl)amino]cyclohex-1-enyl}-3-oxopropionic Acid Allyl Ester (13b)

To a solution of **12b** (3.45 g, 7.74 mmol) in CH_2Cl_2 (77.4 mL) at r.t. was added Dess–Martin periodinane (3.61 g, 8.51 mmol), and the reaction mixture was stirred at the same temperature. After 12 h, the reaction was quenched by the addition of aq $Na_2S_2O_3$ (40 mL) and sat. aq $NaHCO_3$ (40 mL) After dilution with Et_2O (40 mL), the resulting mixture was stirred for 1 h, and then extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (100 mL) and dried (Na_2SO_4). After concentration in vacuo, the obtained residue was purified by flash column chromatography to give **13b** (3.33 g, 7.51 mmol, 97%) as a pale yellow oil; $[\alpha]_D^{23}$ –39.9 (*c* 1.45, $CHCl_3$); 95% ee.

IR (ATR): 2936, 1742, 1681, 1511, 1456, 1402, 1364, 1301, 1242, 1162, 1034, 986 cm^{-1}.

^1H NMR ($CDCl_3$, 55 °C): δ = 1.42 (s, 9 H), 1.40–1.55 (m, 1 H), 1.55–1.70 (m, 2 H), 1.71–1.87 (m, 1 H), 2.10–2.27 (m, 2 H), 3.35–3.52 (m, 1 H), 3.64 (d, *J* = 15.2 Hz, 1 H), 3.78 (s, 3 H), 4.19 (d, *J* = 15.2 Hz, 1 H), 4.31–4.50 (m, 1 H), 4.55–4.70 (m, 2 H), 4.70–4.79 (m, 1 H), 5.15–5.39 (m, 2 H), 5.80–6.00 (m, 1 H), 6.72–6.85 (m, 2 H), 6.85–6.94 (m, 1 H), 7.05–7.18 (m, 2 H).

^{13}C NMR ($CDCl_3$, 55 °C): δ = 19.6, 25.6, 28.2 (3 C), 44.7, 49.4, 51.7, 55.0, 65.4, 79.4, 87.2, 113.5 (2 C), 118.1, 128.4, 131.5, 131.7 (2 C), 139.9, 142.9, 155.2, 158.4, 166.9, 192.1.

ESI-HRMS: *m*/*z* Calcd for $C_{25}H_{33}NO_6$ + Na (M + Na^+): 466.2206; found: 466.2185.

(2*S*,8a*S*)-4-Hydroxy-1-(4-methoxybenzyl)-2-propyl-1,2,6,7,8,8a-hexahydroquinoline-3-carboxylic Acid Allyl Ester (15ba)

To a solution of **13b** (718.5 mg, 1.62 mmol) and Et_3SiH (2.59 mL, 16.2 mmol) in CH_2Cl_2 (8.1 mL) at r.t. was added TFA (8.1 mL), and the reaction mixture was stirred at the same temperature for 30 min. After concentration in vacuo, the obtained residue was dissolved in CH_2Cl_2 (13.5 mL) and MeOH (2.7 mL). *n*-Butyraldehyde (**14a**; 0.44 mL, 4.86 mmol), MS 3Å (0.81 g), and $NaHCO_3$ (408.3 mg, 4.86 mmol) were added to the solution, and the reaction mixture was stirred at r.t. After 48 h, the resulting mixture was filtered through a short pad of Celite, and the filtrate was concentration in vacuo. The obtained residue was purified by flash column chromatography to give **15ba** (631.8 mg, 1.59 mmol, 98%) as a yellow oil. The enantiomeric excess was determined by chiral HPLC analysis {DAICEL CHIRALPAK AD-H, hexane–propan-2-ol, 99:1, flow rate: 1 mL/min, t_R 9.6 min [(2*S*,8a*S*)-isomer] and 11.0 min [(2*R*,8a*R*)-isomer], detection at 254 nm}; $[\alpha]_D^{23}$ +44.3 (*c* 2.01, $CHCl_3$); 95% ee.

IR (ATR): 2933, 1649, 1628, 1583, 1509, 1321, 1287, 1239, 1222, 1117, 1073, 1037, 984, 964, 802 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.76 (t, *J* = 7.0 Hz, 3 H), 1.17–1.70 (m, 6 H), 1.79–1.91 (m, 2 H), 2.19–2.30 (m, 2 H), 3.14 (d, *J* = 14.0 Hz, 1 H), 3.43 (dd, *J* = 3.4, 10.2 Hz, 1 H), 3.73 (d, *J* = 14.0 Hz, 1 H), 3.80 (s, 3 H), 3.82–3.93 (m, 1 H), 4.58–4.70 (m, 2 H), 5.12–5.30 (m, 2 H), 5.79–5.94 (m, 1 H), 6.73–6.89 (m, 3 H), 7.18–7.26 (m, 2 H), 12.1 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 13.8, 19.8, 21.9, 26.4, 27.2, 35.4, 51.0, 51.1, 55.2, 55.7, 64.6, 98.9, 113.3 (2 C), 117.5, 128.8, 129.5 (2 C), 132.0, 132.1, 133.2, 158.2, 163.6, 172.5.

ESI-HRMS: *m*/*z* calcd for $C_{24}H_{32}NO_4$ (M + H^+): 398.2331; found: 398.2336.

(2*S*,8a*S*)-1-(4-Methoxybenzyl)-2-propyl-2,3,6,7,8,8a-hexahydro-1*H*-quinolin-4-one [(+)-16a]

To a solution of **15ba** (1.41 g, 3.55 mmol) and morpholine (3.1 mL, 35.5 mmol) in THF (36 mL) at r.t. was added $Pd(PPh_3)_4$ (41.1 mg, 0.0355 mmol), and the resulting mixture was stirred at the same temperature. After 2 h, 1 M aq HCl (36 mL) was added to the solution, and the resulting mixture was stirred at r.t. for additional 24 h. After the reaction was quenched with aq $NaHCO_3$ (50 mL), the obtained mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL), and dried (Na_2SO_4). After concentration in vacuo, the obtained residue was purified by flash column chromatography to give (+)-**16a** (910.9 mg, 2.91 mmol, 82%) as a yellow oil. The enantiomeric excess was determined by chiral HPLC analysis {DAICEL CHIRALPAK AD-H, hexane–propan-2-ol, 99:1, flow rate: 1 mL/min, t_R 19.5 min [(2*S*,8a*S*)-isomer] and 22.9 min [(2*R*,8a*R*)-isomer], detection at 254 nm}; $[\alpha]_D^{25}$ +9.9 (*c* 1.22, $CHCl_3$); 95% ee.

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IR (ATR): 2930, 1686, 1613, 1509, 1457, 1298, 1241, 1170, 1101, 1034, 830, 807, 731 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.85 (t, *J* = 7.0 Hz, 3 H), 1.15–1.73 (m, 6 H), 1.77–1.89 (m, 1 H), 1.93–2.08 (m, 1 H), 2.16–2.28 (m, 2 H), 2.33 (dd, *J* = 3.0, 17.2 Hz, 1 H), 2.60 (dd, *J* = 6.4, 17.2 Hz, 1 H), 2.90–3.02 (m, 1 H), 3.55–3.70 (m, 1 H), 3.67 (d, *J* = 14.0 Hz, 1 H), 3.73 (d, *J* = 14.0 Hz, 1 H), 3.81 (s, 3 H), 6.79–6.90 (m, 3 H), 7.24–7.33 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 14.1, 19.8, 21.1, 26.1, 28.2, 31.6, 42.2, 52.2, 54.3, 54.5, 55.2, 113.6 (2 C), 129.3 (2 C), 132.3, 137.1, 137.4, 158.5, 199.6.

ESI-HRMS: *m*/*z* calcd for $C_{20}H_{27}NO_2$ + Na (M + Na^+): 336.1940; found: 336.1963.

(2*R*,5*R*,8a*R*)-Trifluoromethanesulfonic Acid 1-(4-Methoxybenzyl)-5-methyl-2-propyl-1,2,3,5,6,7,8,8a-octahydroquinolin-4-yl Ester (19)

To a suspension of CuCN (83.2 mg, 0.927 mmol) in Et_2O (3.3 mL) at –78 °C was added MeLi (1.7 mL, 1.07 M in Et_2O, 1.89 mmol), and the mixture was stirred at the same temperature. After 30 min, a THF solution of (–)-**16a** (97.0 mg, 0.309 mmol in 5.0 mL of THF) was added to the solution, and the resulting mixture was stirred at the same temperature for 30 min. After gradually warming to r.t., the reaction mixture was stirred overnight, and then cooled down to –78 °C again. *N*-(5-Chloro-2-pyridyl)bis(trifluoromethanesulfonimide) (**18**; 364.6 mg, 0.928 mmol) was added to the solution. The reaction was gradually warmed to r.t., and kept stirring overnight. The reaction was quenched with ammonia solution (10 mL), and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), and dried (Na_2SO_4). After concentration in vacuo, the obtained crude residue was purified by flash column chromatography to give **19** (76.5 mg, 0.166 mmol, 54%) as a pale yellow oil; $[\alpha]_D^{24}$ + 5.4 (*c* 1.01, $CHCl_3$).

IR (ATR): 2933, 1510, 1410, 1242, 1203, 1139, 1092, 1038, 966, 928, 903, 870, 837 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.93 (t, *J* = 7.2 Hz, 3 H), 1.03 (d, *J* = 7.2 Hz, 3 H), 1.40–1.70 (m, 9 H), 1.71–1.82 (m, 1 H), 2.10–2.23 (m, 1 H), 2.32 (dd, *J* = 8.8, 16.0 Hz, 1 H), 2.97–3.09 (m, 1 H), 3.10–3.21 (m, 2 H), 3.28 (d, *J* = 13.4 Hz, 1 H), 3.66 (d, *J* = 13.4 Hz, 1 H), 3.81 (s, 3 H), 6.80–6.92 (m, 2 H), 7.18–7.30 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 13.9, 17.2, 19.8, 20.2, 29.6, 30.0, 32.5, 32.7, 33.8, 49.4, 52.9, 55.2, 55.3, 113.7 (2 C), 118.4 (q, *J* = 317.6 Hz), 129.4 (2 C), 132.0, 135.0, 137.5, 158.5.

ESI-HRMS: *m*/*z* calcd for $C_{22}H_{31}F_3NO_4S$ (M + H^+): 462.1926; found: 462.1929.

Procedures for the Conjugate Addition of Organocopper Reagents to Enone (–)-16a

Method A

To a suspension of CuCN (27.6 mg, 0.308 mmol) in Et_2O (1.1 mL) at –78 °C was added MeLi (0.57 mL, 1.09 M in Et_2O, 0.62 mmol), and the resulting mixture was stirred at the same temperature. After 30 min, a THF solution of (–)-**16a** (32.2 mg, 0.103 mmol in THF 1.7 mL) was added to the solution, and the reaction was stirred at –78 °C for 30 min. After gradually warming to r.t., the reaction mixture was stirred overnight. The reaction was quenched with *tert*-butyl alcohol (1.7 mL), and the mixture was stirred for additional 30 min. Ammonia solution (5 mL) was added to the mixture and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), and dried (Na_2SO_4). After concentration in vacuo, the obtained residue was purified by flash column chromatography to give **20** (13.5 mg, 0.0410 mmol, 40%) and **21** (19.0 mg, 0.0577 mmol, 56%).

Method B

To a suspension of CuI (1.41 g, 7.40 mmol) in THF (34.2 mL) at –78 °C was added MeLi (14.8 mL, 1.0 M in Et_2O, 14.8 mmol), and the resulting mixture was stirred at the same temperature. After 30 min, triisopropylsilyl chloride (1.6 mL, 7.47 mmol) was added to the solution, and the reaction mixture was stirred at the same temperature for additional 30 min. A THF solution of (–)-**16a** (979.6 mg, 2.46 mmol in 15 mL of THF) was added to the solution. The reaction mixture was stirred for 30 min at –78 °C, and then gradually warmed to r.t. After stirring overnight, the reaction was quenched with sat. aq $NaHCO_3$ (40 mL) and the resulting mixture was stirred for 1 h at r.t. A small volume of ammonia solution was added to the suspension to dissolve the solidified copper species. (**Caution!** If a large volume of ammonia solution was added to the suspension, enol silyl ether **22** was converted into **20** rather than **21**.) The resulting mixture was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine (40 mL) and dried (Na_2SO_4). After concentration in vacuo, the obtained residue was dissolved in wet (reagent grade) THF (16 mL). TBAF (8.6 mL, 1.0 M in THF, 8.6 mmol) was added to the solution, and the resulting mixture was stirred for 24 h at r.t. The reaction was quenched with H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), and dried (Na_2SO_4). After concentration in vacuo, the obtained crude residue was purified by flash column chromatography to give **20** (215.1 mg, 0.653 mmol, 27%) and **21** (566.9 mg, 1.72 mmol, 70%).

(2*R*,4a*R*,5*R*,8a*R*)-1-(4-Methoxybenzyl)-5-methyl-2-propyloctahydroquinolin-4-one (20)

Pale yellow oil; $[\alpha]_D^{25}$ –7.5 (*c* 0.86, $CHCl_3$).

IR (ATR): 2929, 2862, 1703, 1611, 1509, 1459, 1300, 1243, 1169, 1147, 1087, 1035, 822 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.81 (t, *J* = 7.2 Hz, 3 H), 0.97 (d, *J* = 7.2 Hz, 3 H), 1.10–1.65 (m, 9 H), 1.91–1.99 (m, 1 H), 2.13 (dd, *J* = 2.0, 14.8 Hz, 1 H), 2.18 (dd, *J* = 3.6, 10.4 Hz, 1 H), 2.48–2.57 (m, 1 H), 2.62 (dd, *J* = 6.0, 14.8 Hz, 1 H), 2.92–3.00 (m, 1 H), 3.14 (dt, *J* = 3.1, 11.2 Hz, 1 H), 3.74 (d, *J* = 14.0 Hz, 1 H), 3.81 (d, *J* = 14.0 Hz, 1 H), 3.81 (s, 3 H), 6.83–6.88 (m, 2 H), 7.26–7.30 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 13.8, 14.0, 19.6, 20.3, 27.1, 32.2, 32.5, 32.8, 42.6, 50.9, 52.9, 55.2, 55.2, 56.7, 113.6 (2 C), 129.3 (2 C), 132.7, 158.5, 210.4.

ESI-HRMS: *m*/*z* calcd for $C_{21}H_{32}NO_2$ (M + H^+): 330.2433; found: 330.2448.

(2*R*,4a*S*,5*R*,8a*R*)-1-(4-Methoxybenzyl)-5-methyl-2-propyloctahydroquinolin-4-one (21)

Pale yellow oil; $[\alpha]_D^{24}$ +27.3 (*c* 0.88, $CHCl_3$).

IR (ATR): 2926, 2855, 1701, 1509, 1457, 1376, 1301, 1241, 1173, 1095, 1035, 828 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.81 (d, *J* = 7.2 Hz, 3 H), 0.88 (t, *J* = 7.0 Hz, 3 H), 1.10–1.75 (m, 10 H), 2.23 (dd, *J* = 8.0, 13.4 Hz, 1 H), 2.25–2.35 (m, 1 H), 2.39 (dd, *J* = 4.0, 13.4 Hz, 1 H), 2.45–2.57 (m, 1 H), 3.05–3.21 (m, 2 H), 3.62 (d, *J* = 13.4 Hz, 1 H), 3.80 (d, *J* = 13.4 Hz, 1 H), 3.82 (s, 3 H), 6.81–6.95 (m, 2 H), 7.26–7.35 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 14.1, 18.6, 19.4, 20.4, 27.6, 28.1, 30.4, 32.4, 44.0, 49.2, 55.1, 55.2, 55.2, 55.6, 113.7 (2 C), 129.3 (2 C), 132.1, 158.5, 212.0.

ESI-HRMS: *m*/*z* calcd for $C_{21}H_{32}NO_2$ (M + H^+): 330.2433; found: 330.2448.

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(2*R*,4a*S*,5*R*,8a*R*)-Trifluoromethanesulfonic Acid 1-(4-Methoxybenzyl)-5-methyl-2-propyl-1,2,4a,5,6,7,8,8a-octahydroquinolin-4-yl Ester (23)

To a solution of *i*-Pr_2NH (0.20 mL, 1.43 mmol) in THF (7.0 mL) at –78 °C was added *n*-BuLi (0.91 mL, 1.56 M in *n*-hexane, 1.42 mmol), and the reaction mixture was stirred at the same temperature. After 30 min, a THF solution of **21** (232.7 mg, 0.706 mmol in 4.0 mL of THF) was added to the solution, and the mixture was stirred at –78 °C. After 1 h, **18** (831.7 mg, 2.12 mmol) was added to the solution, and the resulting mixture was stirred at the same temperature for 30 min. After gradually warming to r.t., the mixture was stirred overnight, and quenched with ammonia solution (10 mL). The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic layers were washed with brine (20 mL) and dried (Na_2SO_4). After concentration in vacuo, the obtained crude residue was purified by flash column chromatography to give **23** (283.0 mg, 0.613 mmol, 87%) as a pale yellow oil; $[\alpha]_D^{24}$ –44.8 (*c* 1.03, $CHCl_3$).

IR (ATR): 2934, 1510, 1459, 1415, 1244, 1203, 1170, 1140, 1084, 1036, 948, 906, 853 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.86 (d, *J* = 7.2 Hz, 3 H), 0.88 (t, *J* = 7.0 Hz, 3 H), 1.15–1.57 (m, 7 H), 1.60–1.72 (m, 2 H), 2.22–2.35 (m, 1 H), 2.49–2.60 (m, 1 H), 2.95–3.05 (m, 1 H), 3.28–3.36 (m, 1 H), 3.41–3.55 (m, 1 H), 3.77–3.83 (m, 4 H), 3.85 (d, *J* = 13.6 Hz, 1 H), 5.64–5.66 (m, 1 H), 6.80–6.93 (m, 2 H), 7.18–7.26 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 14.4, 17.4, 18.3, 19.0, 19.7, 28.3, 28.7, 34.1, 45.3, 51.0, 51.5, 55.0, 55.1, 113.7 (2 C), 118.6 (q, *J* = 318.9 Hz), 121.3, 129.0 (2 C), 131.6, 149.5, 158.5.

ESI-HRMS: *m*/*z* calcd for $C_{22}H_{31}F_3NO_4S$ (M + H^+): 462.1926; found: 462.1933.

(+)-2-*epi*-*cis*-195A

To a solution of **23** (35.1 mg, 0.076 mmol) in MeOH (1.5 mL) and 2 M HCl–MeOH (0.076 mL) was added $Pd(OH)_2$/C (7.5 mg, 20 wt% Pd on carbon), and the reaction mixture was stirred under an H_2 atmosphere at r.t. After 24 h, the resulting mixture was filtered through a short pad of Celite, and the filtrate was evaporated under reduced pressure. The obtained crude residue was purified by flash column chromatography to give (+)-2-*epi*-cis-195A·HCl. The pure (+)-2-*epi*-cis-195A·HCl was dissolved in EtOAc (1.6 mL) and sat. aq $NaHCO_3$ (1.6 mL) was added to the solution. The resulting mixture was stirred at r.t. for 30 min. The aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4). Evaporation of the organic solvent gave pure (+)-2-*epi*-*cis*-195A (13.7 mg, 0.0701 mmol, 93%) as pale brown oil; $[\alpha]_D^{22}$ +18.1 (*c* 0.25, MeOH).

IR (ATR): 2926, 2871, 1457, 1379, 1287, 1238, 1163, 1029 cm^{-1}.

^1H NMR ($CDCl_3$) δ = 0.91 (t, *J* = 6.6 Hz, 3 H), 1.00 (d, *J* = 7.2 Hz, 3 H), 1.08–1.90 (m, 16 H), 2.85–3.00 (m, 1 H), 2.95 (br s, 1 H), 3.21 (dt, *J* = 3.9, 10.8 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 14.1, 19.2, 19.2, 20.3, 24.9, 27.5, 28.1, 30.6, 32.5, 37.6, 41.3, 49.8, 50.3.

ESI-HRMS: *m*/*z* calcd for $C_{13}H_{26}N$ (M + H^+): 196.2065; found: 196.2048.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournal/toc/synthesis.

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