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Enantioselective Syntheses of the Alkaloids *cis*-195A (Pumiliotoxin C) and *trans*-195A Based on Multiple Applications of Asymmetric Catalysis

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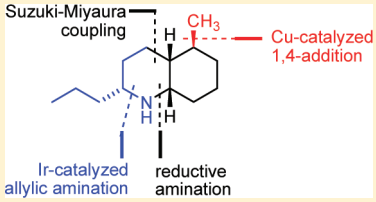
Supporting Information

ABSTRACT: Short enantio- and diastereoselective syntheses of the decahydroquinoline alkaloids *cis*- (pumiliotoxin C) and *trans*-**195A** are presented. Key steps are an enantioselective iridium-catalyzed allylic amination, a Suzuki–Miyaura coupling, a catalyst-controlled copper-catalyzed 1,4-addition, and a reductive amination.



Decahydroquinolines are found in skin secretions of dendrobatid poison-dart frogs and in other amphibian skins.[1] These relatively nontoxic alkaloids have been found to interact with ion channels[2] and are noncompetitive blockers of nicotinic acetylcholine receptors.[3] Because of their interesting biological activity and poor availability, stereoselective syntheses of decahydroquinoline alkaloids have attracted considerable attention. Since the isolation of the most prominent representative *cis*-**195A** (formerly designated pumiliotoxin C, Figure 1) from skin secretions of *Dendrobates*

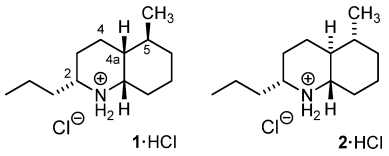
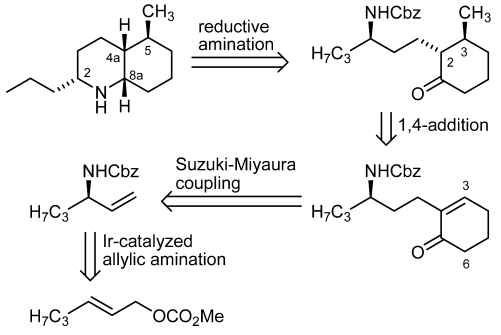


Figure 1. Structures of (+)-*cis*-**195A**·HCl (**1**·HCl) (pumiliotoxin C hydrochloride)[10] and (−)-*trans*-**195A**·HCl (**2**·HCl).

pumilio in 1969[4] and the determination of the absolute configuration in 1977,[5] about 50 alkaloids of this structural class have been identified.[1] The diastereomer *trans*-**195A** (Figure 1) was isolated in trace amounts from *Epipedobates bassleri* in 1999,[6] and the absolute configuration was determined by Blechert et al. in 2005 via an enantioselective synthesis.[7] While many stereoselective syntheses of *cis*-**195A** have been reported,[8] routes based on asymmetric catalysis are rare.[9] In view of this observation, we are pleased to present the shortest (5 steps) synthesis so far, making use of two chiral catalyst-controlled steps.

Our strategy is described as retrosynthesis in Scheme 1. An enantioselective Ir-catalyzed allylic substitution was expected to yield the allylic carbamate with at least 95% ee. For the control of the configuration of the stereogenic centers C4a and C5 of the target, Cu-catalyzed conjugate addition at C3 of the cyclohexenone was planned. It was hoped that recent

Scheme 1. Retrosynthetic Analysis for *cis*-195A



developments in the field would allow chiral catalyst-controlled installation of a methyl group at C3, although 2-substituted enones have rarely been used as substrates. The configuration at the center C2 α to the carbonyl group was expected to be regulated by thermodynamic control. Finally, the reductive amination was expected to be mainly controlled by the center C2.[8b]

The Ir-catalyzed allylic substitution is a reliable method for the synthesis of chiral allylamines starting from easily available monosubstituted allyl carbonates. A variety of C-, N-, O-, and S-nucleophiles can be applied with high degrees of regio- and enantioselectivity.[11] The reaction is particularly well suited for cyclizations.[12]

The allylic amination of carbonate **3** with NH(CHO)Cbz[13] as pronucleophile was carried out under salt-free conditions[14] (Scheme 2, Table 1). Chiral cyclometalated Ir-catalysts[15] were generated in situ from $[Ir(cod)Cl]_2$ (cod = 1,5-cyclooctadiene), a phosphoramidite ligand,[16] and TBD (TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene) as base. The reaction proceeded

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Scheme 2. Iridium-Catalyzed Allylic Amination

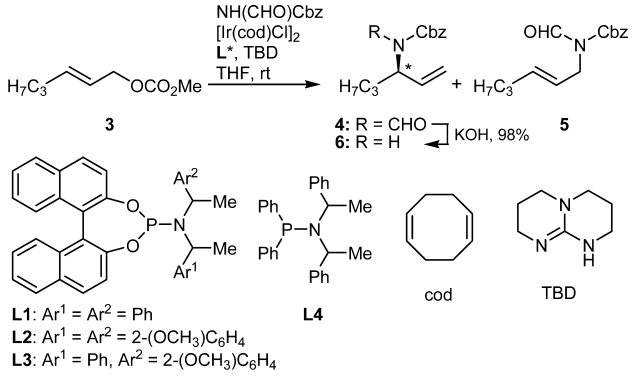


Table 1. Results According to Scheme 2

entry	L*	catalyst[a] (mol %)	time (h)	4/5[b]	yield[c] (%)	ee[d] (%)
1	(*R*,*R*,a*R*)-**L1**	4	1	87:13	91	94[e]
2	(*S*,*S*,a*S*)-**L2**	4	0.5	92:8	83	97
3	(*S*,*S*,a*S*)-**L3**	4	1	90:10	96	96
4[f]	(*R*,*R*,a*R*)-**L2**	1	1.5	92:8	85	96[e]
5[f]	(*S*,*S*,a*S*)-**L3**	1	3	89:11	95	94

[a]4 mol % of catalyst was prepared from $[Ir(cod)Cl]_2$ (2 mol %), **L*** (4 mol %), and TBD (8 mol %). [b]Determined by ^1H NMR of the crude product. [c]Combined yield of regioisomers **4** and **5**. [d]Determined by HPLC. [e]The enantiomer *ent*-**4** was obtained. [f]The reaction was carried out at 50 °C.

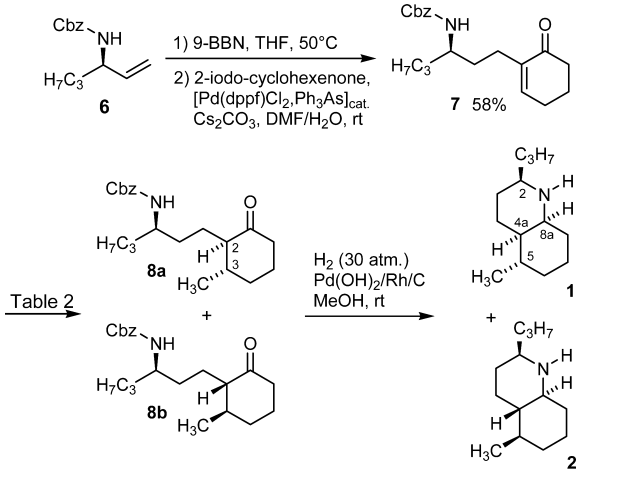
with high regio- and enantioselectivity, allowing a reduction of catalyst loading to 1 mol % (Table 1, entries 4 and 5) without significant loss of enantiomeric excess. Typically, highest selectivities were obtained with Alexakis' ligand **L2**.

Substitution product **4** was obtained in 85% yield after chromatographic purification. The formyl group was cleaved with KOH to give carbamate **6** in excellent yield (Scheme 2).[17] Hydroboration of **6** was carried out with an excess of 9-BBN at 50 °C in order to ensure complete conversion.[13] Subsequent Suzuki–Miyaura coupling[18] with 2-iodocyclohex-2-en-1-one[19] was carried out with $Pd(dppf)Cl_2/Ph_3As$[20] (dppf = 1,1′-bis(diphenylphosphino)ferrocene) as catalyst and Cs_2CO_3 as base (Scheme 3). Removal of 9-BBN-derived impurities required careful chromatographic purification of enone **7**.

The Cu-catalyzed conjugate addition of a methylmetal compound to enone **7** (Scheme 3) generates two new chirality centers, and therefore, four diastereoisomeric products are possible. However, the addition to the enone initially yields an enolate with one new chirality center; the subsequent protonation under thermodynamically controlled conditions is expected to favor the *trans*- over the *cis*-disubstituted cyclohexanone.[21] Thus, mainly the diastereomers **8a** and **8b** are expected as products.

First, substrate control of the reaction was examined. Addition of an achiral cuprate to enone **7** followed by protonation with NH_4Cl yielded a mixture of *trans*-cyclohexanones **8a** and **8b**, which could not be separated. 2,3-*cis*-Isomers of these compounds could not be isolated; NMR spectra of the *trans*-isomers contained signals of maximally 10% impurities, which might have been due to *cis*-isomers. We assume that the protonation of intermediary enolates is thermodynamically controlled under the workup conditions

Scheme 3. Suzuki–Miyaura Coupling, Cu-Catalyzed 1,4-Addition, and Reductive Amination



as anticipated (see above). The mixture was subjected to reductive amination to give the target compounds **1** (formed from **8a**) and **2** (formed from **8b**), which were separable by chiral GC as well as preparative chromatography; at this stage the ee could also be determined. **1** and **2** were obtained in 77% yield in a 2:1 ratio (Table 2, entry 1). Low selectivity was

Table 2. Results from Reactions According to Scheme 3

entry	conditions	yield of **8**[a] (%)	yield (%), ratio **1**/**2**[b]	ee **1**/**2**[c] (%)
1	(1) CuCN, MeMgBr, Et_2O, −30 °C, (2) aq NH_3	75	77, 2:1	97/96
2	(1) CuTC,[d] (*R*,*R*,a*S*)-**L1**, $AlMe_3$, Et_2O, −30 °C, (2) CH_3OH/NH_4Cl	85	80, 5:1	>99/80
3[e]	(1) CuTC,[d] (*R*,*R*,a*S*)-**L1**, $AlMe_3$, Et_2O, −30 °C, (2) CH_3OH/NH_4Cl	72	83, <1:99	−/99
4	(1) CuTC,[d] (*R*,*R*)-**L4**, $AlMe_3$, Et_2O, −30 °C, (2) CH_3OH/NH_4Cl	49	92, 2:1	98/88
5	(1) CuTC,[d] (*S*,*S*)-**L4**, $AlMe_3$, Et_2O, −30 °C, (2) CH_3OH/NH_4Cl	65	82, 1:8	89/98

[a]Combined yield of **8a** and **8b**. [b]Combined yield of **1** and **2**; the ratio **1**/**2** was determined by GC–MS. [c]Determined by chiral GC. [d]TC = thiophene-2-carboxylate. [e]The enantiomer *ent*-**7** was used; thus, *ent*-**8b** and *ent*-**2** were obtained.

expected here, as the chirality center in **7** is far away from the enone moiety. Optical rotations of the products were measured; **1**: $[\alpha]^{20}_D$ −2.2 (*c* 1.34, MeOH), **1**·HCl: $[\alpha]^{20}_D$ +12.9 (*c* 0.36, MeOH), **2**: $[\alpha]^{20}_D$ −31.6 (*c* 0.91, MeOH), **2**·HCl: $[\alpha]^{20}_D$ −26.0 (*c* 0.61, MeOH). Within the range of precision, these values agree with those reported.[7b,8b] The relative configuration of **1** was confirmed by comparison of ^{13}C NMR data with those reported by Daly et al.[22] The ^{13}C NMR data of **2**·HCl matched those reported by Habermehl et al.[8b]

Next, chiral copper catalysts were probed. Trimethylaluminum was used as metal organyl under conditions developed by Alexakis.[23] The addition promoted by **L1** proceeded smoothly to give a 5:1 mixture of **8a** and **8b** in 85% yield (Table 2, entry 2). 2,3-*cis*-Isomers of **8a** and **8b** might have been formed as side products but could not be isolated. The alkaloids **1** and **2** were prepared by reductive amination;[24] separation by column

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chromatography gave **1** in 67% and **2** in 13% yield. Because of double asymmetric induction, the enantiomeric excess of **1** was increased to >99% ee.

For the synthesis of *ent*-**2**, the substrate *ent*-**7** was prepared from *ent*-**4** in the way described above, and the addition and subsequent reductive amination were run as with **7**. Remarkably, only the product *ent*-**2** was obtained in 72% yield. Thus, a ratio *ent*-**8a**/*ent*-**8b** of 1:99 was achieved in the conjugate addition step (Table 2, entry 3). In the reductive amination, the center C2 of the hydroquinoline intermediate constitutes the control element for the configuration at C8a.

Phosphoramidite ligands have been found to react with $AlMe_3$ to form aminophosphine ligands, which are the active species in the cuprate addition reaction.[25] In order to avoid this complication, the cuprate addition reaction was also carried out with simplephos ligands **L4** (Table 2, entries 4 and 5).[26] With respect to reactivity and diastereoselectivity, the results with these were inferior to those obtained with the phosphoramidite ligand **L1**.

In conclusion, we have developed a 5-step enantioselective route yielding the decahydroquinoline alkaloids *cis*- (pumiliotoxin C) and *trans*-**195A**, each in total yields of 28%.[27] Every bond-forming step is controlled by catalysis. The route comprises an asymmetric Ir-catalyzed allylic amination, a Pd-catalyzed Suzuki–Miyaura coupling, a Cu-catalyzed conjugate addition, and a Pd-catalyzed reductive amination. Because of double asymmetric induction, enantiomeric excesses of the final products were very high (≥99%).

EXPERIMENTAL SECTION

Benzyl Formyl[(1*R*)-propylprop-2-en-1-yl]carbamate (4) and Benzyl Formyl[(2*E*)-hex-2-en-1-yl]carbamate (5). Success with the following procedure requires dry TBD (dried in a desiccator over KOH). Under an atmosphere of argon, a solution of $[Ir(cod)Cl]_2$ (14.0 mg, 20.8 μmol), dry TBD (11.5 mg, 82.6 μmol), and (*S*,*S*,a*S*)-**L3** (22.8 mg, 40.1 μmol) in dry THF (1.5 mL) was stirred at rt for 20 min. Carbonate **3** (158 mg, 999 μmol) and (HCO)NH(Cbz)[13] (206.3 mg, 1.151 mmol) were added, and the solution was stirred at rt. Complete conversion was reached after 1 h [TLC: R_f(**3**) = 0.57, R_f(**4**) = 0.52, R_f(**5**) = 0.40, PE/EtOAc 10:1]. The solvent was removed in vacuo, and the ratio **4**/**5** = 90:10 was determined by ^{1}H NMR of the crude product. Flash chromatography (PE/EtOAc 20:1) yielded pure **4** (223 mg, 85%) and **5** (27 mg, 10%) as colorless oils.

4: $[\alpha]^{20}_D$ +6.8 (*c* 0.73, in $CHCl_3$); HPLC (Chiralpak AD-H, *n*-hexane/*i*PrOH 99.5:0.5, flow 0.5 mL min^{-1}, λ 210 nm) t_R((−)-(*S*)-**4**) 22.0 min, t_R((+)-(*R*)-**4**) 22.7 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (3 H, t, *J* = 7.3 Hz), 1.13–1.33 (2 H, m), 1.68–1.94 (2 H, m), 4.94 (1 H, td, *J* = 7.3, 7.7 Hz), 5.08–5.20 (2 H, m), 5.25 (1 H, d, *J* = 12.2 Hz), 5.30 (1 H, d, *J* = 12.2 Hz), 6.06 (1 H, ddd, *J* = 7.2, 10.2, 17.3 Hz), 7.30–7.42 (5 H, m), 9.26 (1 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7 (CH_3), 19.5 (CH_2), 33.8 (CH_2), 54.9 (CH), 68.7 (CH_2), 117.4 (CH_2), 128.4 (CH), 128.73 (CH), 128.79 (CH), 134.7 (C_q), 136.5 (CH), 153.8 (C_q), 162.9 (CH); HR-MS (FAB+) calcd for $C_{15}H_{19}NO_3$ $[M]^+$ 261.1365, found 261.1362.

5: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (3 H, t, *J* = 7.4 Hz), 1.34 (2 H, qt, *J* = 6.8, 7.4 Hz), 1.95 (2 H, td, *J* = 6.8, 6.6 Hz), 4.18 (2 H, dd, *J* = 6.2, 0.9 Hz), 5.29 (2 H, s), 5.39 (1 H, dtt, *J* = 15.3, 6.3, 1.3 Hz), 5.63 (1 H, dtt, *J* = 14.8, 6.9, 1.1 Hz), 7.34–7.40 (5 H, m), 9.23 (1 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7 (CH_3), 22.1 (CH_2), 34.2 (CH_2), 42.5 (CH_2), 68.8 (CH_2), 123.5 (CH), 128.5 (CH), 128.83 (CH), 128.89 (CH), 134.8 (C_q), 135.2 (CH), 154.0 (C_q), 162.5 (CH); HR-MS (FAB+) calcd for $C_{15}H_{20}NO_3$ $[M + H]^+$ 262.1443, found 262.1431.

Benzyl [(1*R*)-1-Propylprop-2-en-1-yl]carbamate (6). KOH (46 mg, 0.82 mmol) was added to a solution of **4** (1.025 g, 3.922 mmol) in methanol (25 mL) at rt. Complete conversion was reached after 13 h [TLC: R_f(**4**) = 0.52, R_f(**6**) = 0.34, PE/EtOAc 10:1]. The solvent was removed in vacuo, and the residue was purified by flash chromatography (PE/EtOAc 10:1) to yield **6** (900 mg, 98%) as colorless needles (mp 61–62 °C (EtOAc/PE)): $[\alpha]^{20}_D$ +8.7 (*c* 0.63, $CHCl_3$), lit.[17c] for *ent*-**6** $[\alpha]^{26}_D$ −10.1 (*c* 0.79, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (3 H, t, *J* = 7.2 Hz), 1.29–1.55 (4 H, m), 4.11–4.24 (1 H, m), 4.55–4.75 (1 H, br s), 5.06–5.12 (3 H, m), 5.16 (1 H, d, *J* = 17.3 Hz), 5.75 (1 H, ddd, *J* = 16.9, 10.4, 5.8 Hz), 7.29–7.40 (5 H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0 (CH_3), 19.0 (CH_2), 37.4 (CH_2), 53.3 (CH), 66.8 (CH_2), 114.7 (CH_2), 128.2 (CH), 128.7 (CH), 136.7 (C_q), 138.9 (CH), 156.0 (C_q); HR-MS (ESI +) calcd for $C_{14}H_{19}NNaO_2$ $[M + Na]^+$ 256.13080, found 256.13094.

Benzyl {(1*R*)-1-[2-(6-Oxocyclohex-1-en-1-yl)ethyl]butyl}-carbamate (7). 2-Iodocyclohex-2-en-1-one was prepared according to ref 19 and purified by column chromatography immediately before use. Under an atmosphere of argon, a solution of **6** (450 mg, 1.92 mmol) and 9-BBN (470 mg, 3.85 mmol) in dry THF (4 mL) was heated at 50 °C. Complete conversion was reached after 3.5 h [TLC: R_f(**6**) = 0.44, R_f(**7**) = 0.25, PE/EtOAc 3:1]. After cooling to rt, the solution was added to a suspension of Pd(dppf)Cl_2 (70 mg, 96 μmol), Ph_3As (59 mg, 0.19 mmol), Cs_2CO_3 (1.16 g, 3.56 mmol), 2-iodocyclohex-2-en-1-one (472 mg, 2.11 mmol), and degassed DMF/H_2O 15:1 (6 mL). The suspension was stirred at rt for 16 h. Then, water (5 mL) was added, and the solution was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (PE/Et_2O 3:1) yielded **7** (370 mg, 58%) as pale orange amorphous solid: $[\alpha]^{20}_D$ +1.3 (*c* 1.04, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (3 H, t, *J* = 6.8 Hz), 1.25–1.52 (5 H, m), 1.53–1.66 (1 H, m), 1.88–2.00 (2 H, m), 2.06–2.19 (1 H, m), 2.20–2.35 (3 H, m), 2.36–2.43 (2 H, m), 3.48–3.68 (1 H, m), 4.66 (1 H, d, *J* = 8.9 Hz), 5.03–5.17 (2 H, m), 6.72 (1 H, t, *J* = 3.5 Hz), 7.26–7.38 (5 H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1 (CH_3), 19.1 (CH_2), 23.2 (CH_2), 26.1 (CH_2), 26.5 (CH_2), 34.1 (CH_2), 37.7 (CH_2), 38.6 (CH_2), 50.9 (CH), 66.5 (CH_2), 128.1 (CH), 128.6 (CH), 136.9 (C_q), 139.2 (C_q), 146.0 (CH), 156.2 (C_q), 199.6 (C_q); HR-MS (ESI+) calcd for $C_{20}H_{28}NO_3$ $[M + H]^+$ 330.20637, found 330.20661.

Benzyl ((1*R*)-1-{2-[(1″*R*,2″*S*)-2-Methyl-6-oxocyclohexyl]-ethyl}butyl)carbamate (8a) and Benzyl ((1*R*)-1-{2-[(1″*S*, 2″*R*)-2-Methyl-6-oxocyclohexyl]ethyl}butyl)carbamate (8b). *Substrate-Controlled 1,4-Addition According to Table 2, Entry 1.* Under an atmosphere of argon, methylmagnesium bromide (3 M in Et_2O, 0.63 mL, 1.9 mmol) was added dropwise to a suspension of CuCN (70 mg, 0.78 mmol) in dry Et_2O (10 mL) at −40 °C. The suspension was allowed to warm to −20 °C and stirred for 3.5 h. It was then cooled to −30 °C, and a solution of **7** (129 mg, 392 μmol) in dry Et_2O (5 mL) was added dropwise. Complete conversion was reached after 20 h at −30 °C [TLC: R_f(**7**) = 0.25, R_f(**8**) = 0.36, PE/EtOAc 3:1]. Saturated aqueous NH_3 (5 mL) and aqueous NH_4Cl (5 mL) were added, and the solution was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica (PE/EtOAc 5:1) yielded a mixture of **8a** and **8b** (102 mg, 75%) as colorless needles; separation by chromatography was not accomplished. The ratio **8a**/**8b** 2:1 is deduced from the ratio of **1** and **2** (GC–MS) obtained after reductive amination.

Mixture of **8a** and **8b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (3 H, t, *J* = 5.9 Hz), 1.02 (3 H, d, *J* = 6.4 Hz), 1.16–1.72 (11 H, m), 1.77–1.90 (1 H, m), 1.92–2.06 (2 H, m), 2.17–2.40 (2 H, m), 3.50–3.66 (1 H, m), 4.61–4.86 (1 H, m), 5.03–5.19 (2 H, m), 7.24–7.42 (5 H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1 (CH_3), 19.00 (CH_2), 19.08 (CH_2), 20.6 (CH_3), 22.9 (CH_2), 25.7 (CH_2), 25.9 (CH_2), 32.4 (CH_2), 32.8 (CH_2), 33.5 (CH_2), 33.6 (CH_2), 37.7 (CH_2), 38.0 (CH_2), 38.2 (CH), 38.8 (CH), 41.7 (CH_2), 41.9 (CH_2), 51.3 (CH), 51.7 (CH), 56.9 (CH), 57.1 (CH), 66.4 (CH_2), 128.00 (CH), 128.02 (CH), 128.5 (CH), 136.9 (C_q), 156.3 (C_q), 213.1 (C_q), 213.2 (C_q); HR-MS (ESI+) calcd for $C_{21}H_{31}KNO_3$ $[M + K]^+$ 384.19355, found 384.19392.

Reagent-Controlled 1,4-Addition According to Table 2, Entry 2. Under an atmosphere of argon, a solution of CuTC (1.3 mg, 6.8 μmol) and (*R*,*R*,a*S*)-**L1** (6.7 mg, 12 μmol) in dry Et_2O (1 mL) was stirred for 30 min at rt. The solution was cooled to −30 °C, and $AlMe_3$

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(2 M in hexane, 0.31 mL, 0.62 mmol) and **7** (102.9 mg, 312.3 μmol) were added successively. Complete conversion was reached after 19 h at −30 °C. MeOH (0.1 mL) and aqueous NH_4Cl (3 mL) were added, and the solution was allowed to warm to rt. The aqueous layer was separated and extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (PE/EtOAc 5:1) yielded a mixture of **8a** and **8b** (91.5 mg, 85%) as colorless needles; separation by chromatography was not accomplished. The ratio **8a**/**8b** >5:1 is deduced from the ratio of **1** and **2** (GC−MS) obtained after reductive amination.

Benzyl ((1*S*)-1-{2-[(1″*R*, 2″*S*)-2-Methyl-6-oxocyclohexyl]-ethyl}butyl)carbamate (*ent*-8b). *Reagent-Controlled 1,4-Addition According to Table 2, Entry 3.* Under an atmosphere of argon, a solution of CuTC (1.4 mg, 7.2 μmol) and (*R*,*R*,a*S*)-**L1** (7.8 mg, 14 μmol) in dry Et_2O (0.5 mL) was stirred for 30 min at rt and was then cooled to −30 °C. $AlMe_3$ (2 M in hexane, 0.4 mL, 0.8 mmol) and a solution of *ent*-**7** (100 mg, 304 μmol) in dry Et_2O (1 mL) were added successively. Complete conversion was reached after 19 h at −30 °C. MeOH (1 mL) and aqueous NH_4Cl (2 mL) were added, and the mixture was allowed to warm to rt. The aqueous layer was separated and extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (PE/EtOAc 5:1) yielded *ent*-**8b** (75 mg, 72%) as colorless needles (mp 86−88 °C (EtOAc/PE)). The product was diastereomerically and enantiomerically pure according to the determination after reductive amination.

ent-**8b**: $[\alpha]^{20}_D$ +3.3 (*c* 0.43, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (3 H, t, *J* = 6.7 Hz), 1.02 (3 H, d, *J* = 6.4 Hz), 1.24−1.72 (11 H, m), 1.78−1.88 (1 H, m), 1.92−2.06 (2 H, m), 2.20−2.40 (2 H, m), 3.50−3.66 (1 H, m), 4.69 (1 H, d, *J* = 8.8 Hz), 5.04−5.17 (2 H, m), 7.25−7.40 (5 H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1 (CH_3), 19.1 (CH_2), 20.6 (CH_3), 22.9 (CH_2), 25.9 (CH_2), 32.8 (CH_2), 33.7 (CH_2), 38.1 (CH_2), 38.8 (CH), 41.9 (CH_2), 51.4 (CH), 57.0 (CH), 66.5 (CH_2), 128.06 (CH), 128.08 (CH), 128.6 (CH), 137.0 (C_q), 156.4 (C_q), 213.3 (C_q).

(2*R*,4a*R*,5*S*,8a*S*)-5-Methyl-3-propyldecahydroquinoline (1) and (2*R*,4a*S*,5*R*,8a*S*)-5-Methyl-3-propyldecahydroquinoline (2). In this experiment, a mixture of **8a**/**8b** prepared via substrate control (Table 2, entry 1) was used. A suspension of **8a**/**8b** (136 mg, 394 μmol, **8a**/**8b** 2:1), $Pd(OH)_2$/C (27.0 mg), and Rh/C (6.8 mg) in MeOH (4 mL) was vigorously stirred under an atmosphere of hydrogen (30 bar). Complete conversion was reached after 17 h at rt [TLC: R_f(**8**) = 0.36, R_f(**1**,**2**) = 0.00, PE/EtOAc 3:1]. Insoluble material was removed by filtration through a pad of silica, and the solution was concentrated in vacuo. The ratio **1**/**2** 2:1 was determined by GC−MS. Purification by flash chromatography (PE/NEt_3 95:5, R_f(**1**) = 0.61, R_f(**2**) = 0.47) yielded **1** (40.5 mg, 53%) and **2** (18.3 mg, 24%) as colorless oils. Crystalline hydrochlorides were obtained in quantitative yield by treatment with HCl (5% in MeOH) followed by evaporation.

1: $[\alpha]^{20}_D$ −2.2 (*c* 1.34, MeOH); GC (Chrompack β-CD, 130 °C isothermal) t_R((+)-(2*S*,4a*S*,5*R*,8a*R*)-**1**) 13.1 min, t_R((−)-(2*R*,4a*R*,5*S*,8a*S*)-**1**) 14.4 min; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.83 (3 H, d, *J* = 6.6 Hz), 0.90 (3 H, t, *J* = 7.0 Hz), 0.94−1.03 (1 H, m), 1.05−1.14 (2 H, m), 1.22−1.49 (9 H, m), 1.50−1.71 (4 H, m), 1.77−1.90 (1 H, m), 1.90−1.99 (1 H, m), 2.53 (1 H, dtd, *J* = 11.4, 5.8, 2.7 Hz), 2.84 (1 H, q, *J* = 2.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.5 (CH_3), 19.3 (CH_2), 20.1 (CH_3), 21.4 (CH_2), 27.2 (CH_2), 27.54 (CH), 27.55 (CH_2), 33.6 (CH_2), 36.1 (CH_2), 39.9 (CH_2), 42.8 (CH), 56.1 (CH), 57.9 (CH); HR-MS (ESI+) calcd for $C_{13}H_{26}N$ $[M + H]^+$ 196.20598, found 196.20600.

1·HCl: $[\alpha]^{20}_D$ +12.9 (*c* 0.36, MeOH), lit.[8b] for *ent*-**1**·HCl $[\alpha]^{20}_D$ −12.9 (*c* 0.6, MeOH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0 (CH_3), 19.3 (CH_2), 19.9 (CH_3), 20.7 (CH_2), 23.3 (CH_2), 25.4 (CH_2), 27.3 (CH), 29.4 (CH_2), 34.6 (CH_2), 35.0 (CH_2), 41.0 (CH), 58.3 (CH), 60.4 (CH).

2: $[\alpha]^{20}_D$ −31.6 (*c* 0.91, MeOH), lit.[7b] for *ent*-**2** $[\alpha]^{24}_D$ +27.4 (*c* 0.56, MeOH); GC (Chrompack β-CD, 130 °C isothermal) t_R((+)-(2*S*,4a*R*,5*S*,8a*R*)-**2**) 16.0 min, t_R((−)-(2*R*,4a*S*,5*R*,8a*S*)-**2**) 16.4 min; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.69 (1 H, qd, *J* = 10.1, 3.5 Hz), 0.85−0.94 (1 H, m), 0.87 (3 H, d, *J* = 6.5 Hz), 0.91 (3 H, t, *J* = 6.8 Hz), 1.00 (1 H, qd, *J* = 12.4, 3.6 Hz), 1.04−1.13 (2 H, m), 1.21−1.39 (6 H, m), 1.59−1.67 (2 H, m), 1.68−1.74 (2 H, m), 1.97 (1 H, dq, *J* = 12.6, 3.2 Hz), 2.17 (1 H, ddd, *J* = 10.5, 10.1, 3.6 Hz), 2.46−2.53 (1 H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4 (CH_3), 19.31 (CH_3), 19.34 (CH_2),[28] 24.9 (CH_2), 29.2 (CH_2), 33.2 (CH_2), 34.1 (CH_2), 35.8 (CH_2), 36.3 (CH), 39.6 (CH_2), 48.7 (CH), 56.7 (CH), 61.5 (CH); HR-MS (ESI +) calcd for $C_{13}H_{26}N$ $[M + H]^+$ 196.20598, found 196.20615.

2·HCl: $[\alpha]^{20}_D$ −26.0 (*c* 0.61, MeOH), lit.[8b] $[\alpha]^{20}_D$ −27.3 (*c* 0.6, MeOH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9 (CH_3), 18.89 (CH_3), 18.90 (CH_2), 24.2 (CH_2), 27.3 (CH_2), 28.1 (CH_2), 30.0 (CH_2), 34.3 (CH_2), 35.1 (CH_2), 36.6 (CH), 44.6 (CH), 58.3 (CH), 61.8 (CH).

(2*R*,4a*R*,5*S*,8a*S*)-5-Methyl-3-propyldecahydroquinoline (1) and (2*R*,4a*S*,5*R*,8a*S*)-5-Methyl-3-propyldecahydroquinoline (2). In this experiment, a mixture of **8a**/**8b** prepared via reagent control (Table 2, entry 2) was used. A suspension of **8a**/**8b** (119.4 mg, 345.6 μmol, **8a**/**8b** >5:1), $Pd(OH)_2$/C (22.7 mg), and Rh/C (5.9 mg) in MeOH (5 mL) was vigorously stirred under an atmosphere of hydrogen (30 bar). Complete conversion was reached after 18 h at rt. Insoluble material was removed by filtration through a pad of silica, and the solution was concentrated in vacuo. The ratio **1**/**2** >5:1 was determined by GC−MS. Purification by flash chromatography (PE/NEt_3 95:5) yielded **1** (45 mg, 67%) and **2** (8.9 mg, 13%) as colorless oils.

(2*S*,4a*R*,5*S*,8a*R*)-5-Methyl-3-propyldecahydroquinoline (*ent*-2). In this experiment, *ent*-**8b** prepared via reagent control (Table 2, entry 3) was used. A suspension of *ent*-**8b** (50 mg, 145 μmol), $Pd(OH)_2$/C (10 mg), and Rh/C (2.9 mg) in MeOH (4 mL) was vigorously stirred under an atmosphere of hydrogen (30 bar). Complete conversion was reached after 16 h at rt. Insoluble material was removed by filtration through a pad of silica, and the solution was concentrated in vacuo to yield *ent*-**2** (23.5 mg, 83%) as colorless oil. *ent*-**2**: $[\alpha]^{20}_D$ +32.4 (*c* 1.1, MeOH). *ent*-**2**·HCl: $[\alpha]^{20}_D$ +25.2 (*c* 0.43, MeOH).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Determination of regio-, enantio-, and diastereoselectivities and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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