Practical Syntheses of Enantiomerically Pure Key Intermediates of Opioid Receptor-like 1 (ORL1) Antagonists

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Abstract: Practical syntheses of enantiomerically pure key intermediates of opioid receptor-like 1 (ORL1) antagonists are described. Our synthetic methodology features the preparation of multigram quantities of seven-membered key intermediate (–)-**3** and six-membered one (–)-**4** without the use of toxic tin reagents. In the case of (–)-**3**, the key step involved diastereoselective reduction using a sterically hindered reducing reagent. Our methodology allows for facile scale-up to afford the products in multigram quantities [in the case of (–)-**4**, >100-g quantities). These convenient approaches facilitate structure–activity relationship studies including in vivo cardiovascular adverse effects.

Key words: ORL1 antagonist, multigram-scale preparation, asymmetric synthesis, cycloalkano[1,2-*b*]pyridines, stereoselective reduction

Since the discovery of a fourth opioid receptor (opioid receptor-like 1, ORL1) followed by the isolation of its endogenous agonist named as nociceptin or orphanin FQ (NC/OFQ),[1] numerous reports have demonstrated the possible involvement of the NC/OFQ-ORL1 system in pain regulation, cognition, anxiety, and cardiovascular systems.[2] Accordingly, several research groups have directed their efforts towards the search for small molecule ORL1 agonists and antagonists.[3] Recently, we reported on highly potent and selective ORL1 antagonists that involve 4-arylpiperidine analogues binding to 5,6,7,8-tetrahydro-9*H*-cyclohepta[*b*]pyridine at the 7-position or 5,6,7,8-tetrahydroquinoline at the 6-position, such as **1** and **2**, respectively. The analogues were prepared by simple alkylation of the corresponding piperidine analogue with the requisite tosylate intermediates (–)-**3** and (–)-**4** (Figure 1).[4] Some analogues in this class, however, exhibited significant inhibitory activity at hERG K^+ channels. Blockade of hERG K^+ channels can result in a drug-acquired long QT syndrome. Our in vitro structure–activity relationship study suggested that the 4-arylpiperidine moiety played a key role in the inhibition of hERG K^+ channels. To further assess the in vivo cardiovascular implications, multigram quantities of key intermediates, (–)-**3** and (–)-**4**, were required. Unfortunately, our previous synthetic routes to the tosylates were, however, not suitable for bulk synthesis for various reasons (Scheme 1 and Scheme 2).[5] In the case of **3**, purification steps following the iodination and radical ring expansion (from **6** to **7** and **7** to **8**, respectively) were laborious, resulting in lowering of the total yield (2.4%) for a one-gram-scale synthesis of (–)-**3**. In the case of **4**, multiple reaction steps were required. Additionally, both synthetic routes required the use of toxic tin reagents, which complicate purification steps and may contaminate the final products. Herein, we report improved synthetic schemes that allow the preparation of enantiomerically pure key intermediates (–)-**3** and (–)-**4** in multigram quantities.

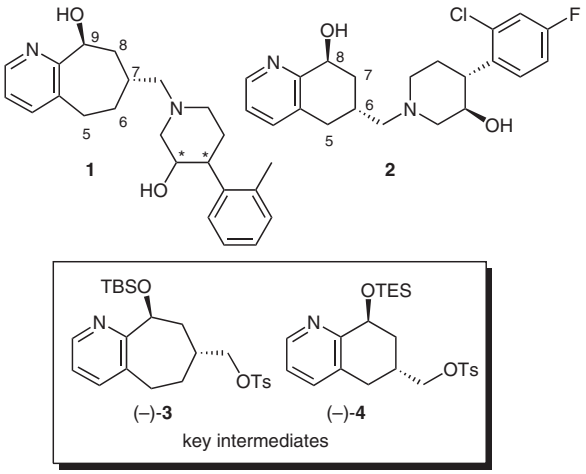
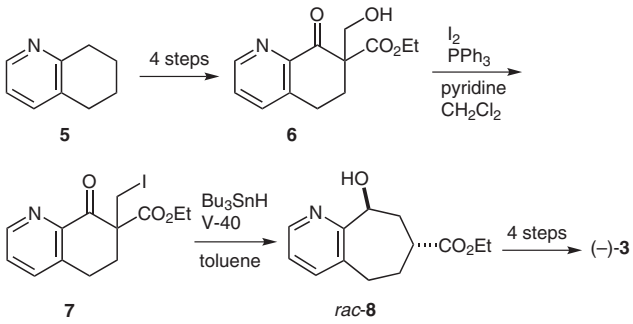


Figure 1 Chemical structures of ORL1 antagonists, **1** and **2**, and their key intermediates, **3** and **4**



Scheme 1 Previous synthetic route for key intermediate (–)-**3**

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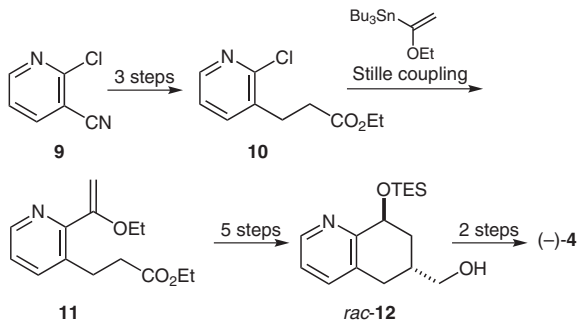
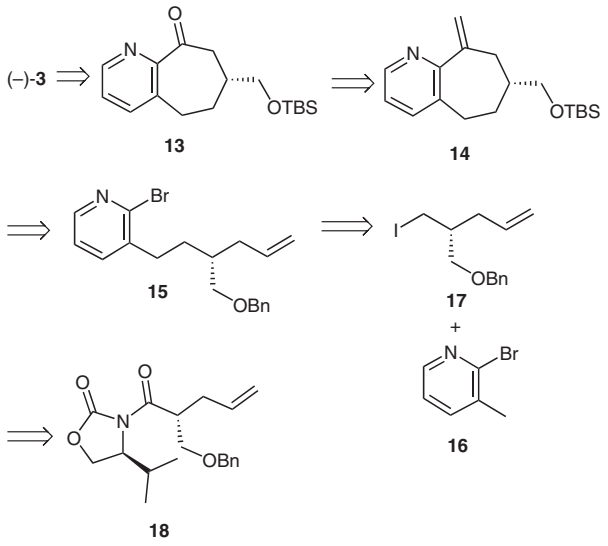


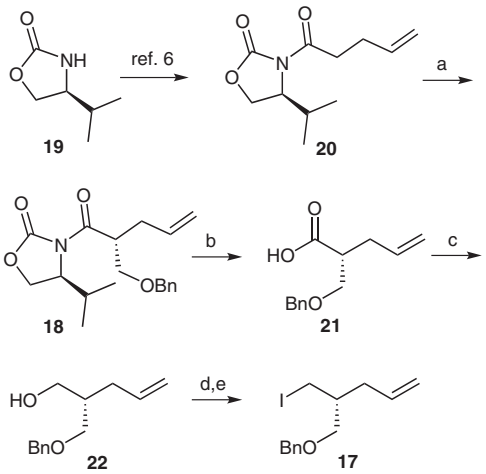
Scheme 2 Previous synthetic route for key intermediate (–)-**4**

The radical ring-expansion reaction of **7** via treatment with excess tributyltin hydride afforded the corresponding *trans*-alcohol **8** with high stereoselectivity (Scheme 1),[5a] hence, we postulated that ketone **13** can be diastereoselectively reduced using an appropriate reducing reagent (Scheme 3). Our synthetic plan for (–)-**3**, therefore, involved the asymmetric synthesis of **13** starting from chiral oxazolidinone derivative **18**.



Scheme 3 Retrosynthetic analysis of (–)-**3**

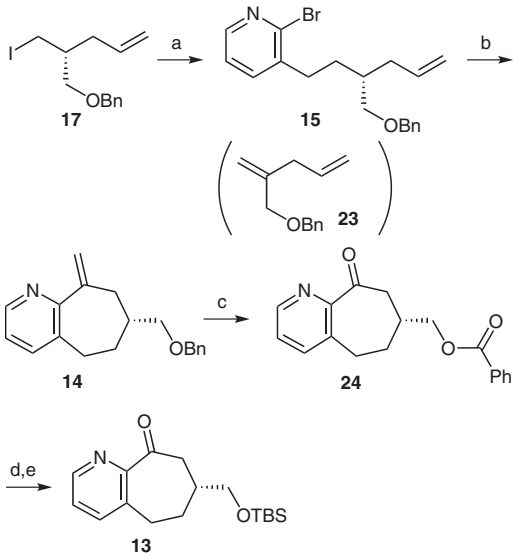
The synthetic route for chiral alkyl iodide **17** is outlined in Scheme 4. The (benzyloxy)methyl group was diastereoselectively introduced into oxazolidinone **20**[6] via Evans method to give **18**.[7,8] The oxazolidinone moiety was cleaved by hydrolysis using the lithium hydroxide–hydrogen peroxide system to afford carboxylic acid **21** in high yield (85% in 3 steps). The carboxylic acid **21** was converted into **22** by treatment with 1,1′-carbonyldiimidazole (CDI) and subsequent addition of sodium borohydride to afford **22** in 77% yield. The optical rotation of **22** {$[\alpha]_D^{26}$ –10.9 (*c* 1.0, $CHCl_3$)} was slightly smaller than that reported in the literature {(*R*)-enantiomer: $[\alpha]_D^{22}$ +13.6 (*c* 0.92, $CHCl_3$)}.[9] The enantiomeric excess of the products will be discussed later. Alcohol **22** was subjected to mesylation under standard conditions followed by iodination with sodium iodide in the presence of sodium hydrogen carbonate to afford iodide **17** in satisfactory yield (92% in 2 steps). It is important to note that this approach allows the preparation of iodide **17** in >100-g scale without column chromatography purification.



Scheme 4 Synthesis of chiral alkyl iodide **17**. *Reagents and conditions*: (a) $TiCl_4$, *i*-Pr_2NEt, $ClCH_2OBn$, CH_2Cl_2, 0–10 °C; (b) 30% H_2O_2, LiOH, THF–H_2O, 5 °C, 85% (from **19**); (c) 1. CDI, DMF, 2. $NaBH_4$, r.t., 77%; (d) MsCl, Et_3N, THF, 5 °C; (e) NaI, $NaHCO_3$, acetone, r.t., 92%.

With iodide **17** in hand, our synthetic efforts were next directed towards the alkylation of the pyridine derivative (Scheme 5). The alkylation of 2-bromo-3-methylpyridine (**16**) with **17** was achieved using two equivalents of the anion prepared from **16** and lithium 2,2,6,6-tetramethylpiperidide in the presence of 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one at –78 to –30 °C to produce adduct **15** in 69% isolated yield.[10] With more than two equivalents of the anion, or using higher temperatures, dehydrohalogenation of **17** occurred, resulting in the significant formation of byproduct **23**. Intramolecular Mizoroki–Heck reaction[11] of **15** using palladium(II) acetate (10 mol%), 1,3-bis(diphenylphosphino)propane (15 mol%), and triethylamine in *N*,*N*-dimethylformamide led to seven-membered *exo*-cyclic alkene **14** in excellent yields (85%). Oxidation of both the benzylic methylene group and the olefinic double bond of **14** in methanol at –50 °C proceeded smoothly with successive bubbling of ozone, to yield **24**. The benzoyl group was cleaved by treatment with sodium hydroxide in aqueous methanol to afford the corresponding alcohol, which was protected by a *tert*-butyldimethylsilyl group using standard procedures. Again, it is important to note that our new synthetic route to **13** is applicable towards multigram-scale synthesis.

With the expedient synthesis of ketone **13** accomplished, the final key step involved conversion of ketone **13** into the desired *trans*-alcohol **25**, as summarized in Table 1. First, radical reduction of **13** by tributyltin hydride in the presence of 1,1′-azobis(cyclohexanecarbonitrile) (V-40) or 2,2′-azobis(isobutyronitrile) was employed, in accordance with our previous experience in radical expansion



Scheme 5 Synthesis of ketone **13**. *Reagents and conditions*: (a) 2-bromo-3-methylpyridine (**16**), LTMP, DMPU, THF, –78 to –30 °C, 69%; (b) $Pd(OAc)_2$, dppp, Et_3N, DMF, 130 °C, 85%; (c) O_3, MeOH, –78 to –50 °C, then Me_2S; (d) aq 1 M NaOH, MeOH, r.t.; (e) TBSCl, imidazole, $CHCl_3$, r.t., 73% (3 steps from **14**).

reactions.[5a] Contrary to our expectations, however, the radical reduction of **13** resulted in a low ratio between the *trans*- and *cis*-alcohols (**25** vs **26**) (entries 1 and 2). The stereochemistry of **25** and **26** were determined by NOE experiments of the corresponding diols, **27** and **27′**, respectively. NOEs were observed between the marked hydrogens of **27** (H_a and H_b) or **27′** (H_c and H_d) and the hydrogens of the hydroxymethyl group at the 7-position (Figure 2). The use of ethanol as a co-solvent (EtOH–toluene, 3:1) dramatically increased the reaction rate while improving the diastereoselectivity (90:10, entry 3), which suggests that tributyltin hydride functioned as a source of a hydride rather than a hydrogen radical.[12] Accordingly, even in the absence of 2,2′-azobis(isobutyronitrile), the reaction afforded **25** with high diastereoselectivity and was complete within ten minutes (76% isolated yield, entry 4). Reduction by sodium borohydride favored the formation of *cis*-alcohol **26** with a ratio of 35:65 (entry 5), suggesting that a sterically hindered reducing reagent is preferable for *trans*-selectivity. As expected, the use of L-Selectride, a highly sterically hindered reducing reagent, enhanced the *trans*-selectivity (98:2, entry 6). Ultimately, the use of LS-Selectride provided the reduction of **13** with excellent diastereoselectivity (99:1) and a satisfactory isolated yield (79%) of alcohol **25** (entry 7).

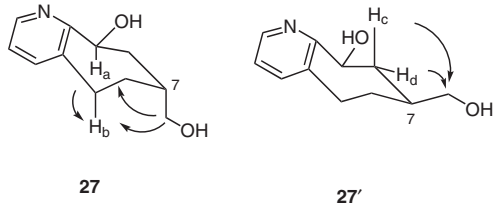


Figure 2 Selected NOEs of diols **27** and **27′**

This diastereoselectivity of the reduction reaction can be explained using density functional theory (DFT) calculations at the B3LYP/6-31G* level.[13] As shown in Figure 3, ketone **13** adopted a most stable conformation, in which the carbonyl group is located out-of-plane to the pyridine ring. Due to this conformation, axial attack by a hydride ion would be hindered by the methylenes of the seven-membered ring and an equatorial attack would be preferred when a sterically hindered reducing reagent is used.

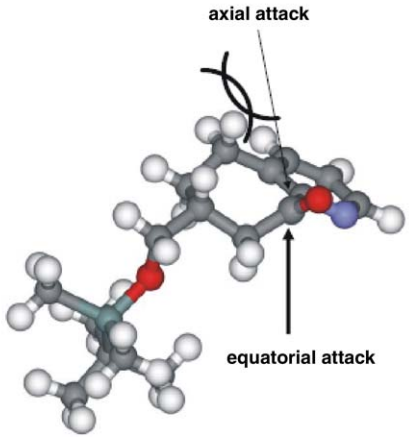
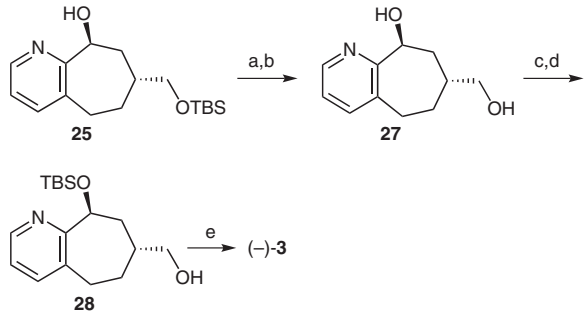


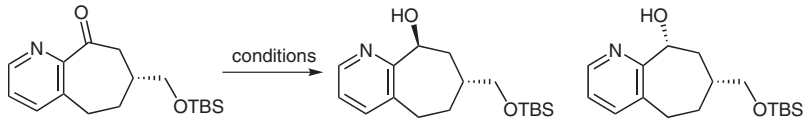
Figure 3 Conformational calculation of ketone **13** at B3LYP/6-31G* level[13]

Conversion of **25** into seven-membered key intermediate (–)-**3** is outlined in Scheme 6. The *tert*-butyldimethylsilyl group of **25** was cleaved by treatment with aqueous hydrochloric acid in tetrahydrofuran to afford diol **27** with 90% ee (chiral HPLC analysis). This result is consistent with that of alcohol **22** (smaller optical rotation as compared to literature, as mentioned above), suggesting that slight racemization occurred during the transformation of oxazolidinone **18** to alcohol **22**. However, recrystallization from methanol and diisopropyl ether afforded enantiomerically pure **27** (>99% ee) in a 68% total yield from **25**. *tert*-Butyldimethylsilyl-protection of the secondary hydroxy group at the 9-position of **27** was carried out by bis-silylation of all hydroxy groups, followed by selective cleavage of the primary *tert*-butyldimethylsilyl group at



Scheme 6 Conversion of **25** into key intermediate (–)-**3**. *Reagents and conditions*: (a) aq 0.5 M HCl, THF, r.t.; (b) recrystallization (MeOH–*i*-Pr_2O), 68% (2 steps); (c) TBSCl, imidazole, DMF, r.t.; (d) aq 0.5 M HCl, THF, r.t., 96% (2 steps); (e) TsCl, Et_3N, DMAP, $CHCl_3$, r.t., 99%.

Table 1 Reduction of Ketone **13**



13 **25** (desired) **26** (undesired)

Entry	Conditions				HPLC area (%)[a]		Isolated yield (%)	
	Reagents (equiv)	Solvent	Temp (°C)	Time	**25**	**26**	**25**	**26**
1	Bu_3SnH (3), V-40[b] (0.3)	toluene	110	3 h	–[c]	–	40	18
2	Bu_3SnH (3), AIBN (0.3)	toluene	90	3 h	60	40	–	–
3	Bu_3SnH (3), AIBN (0.3)	toluene–EtOH (1:3)	90	10 min	90	10	–	–
4	Bu_3SnH (3)	EtOH	78	10 min	94	6	76	–
5	$NaBH_4$ (2)	EtOH	r.t.	0.5 h	35	65	–	–
6	L-Selectride (1.5)	THF	–78	1 h	98	2	–	–
7	LS-Selectride (1.5)	THF	–78	1 h	99	1	79	–

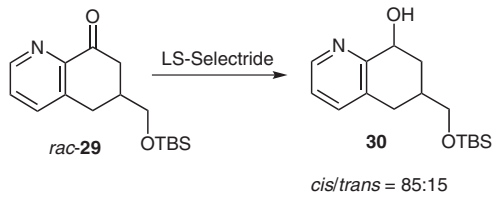
[a] The ratio of **25** and **26** was determined by the area% of RP-HPLC analysis of the reaction mixture.
[b] 1,1′-Azobis(cyclohexanecarbonitrile).
[c] Not determined.

the 7-position and tosylation under standard conditions, to afford key intermediate (–)-**3** in quantitative yield.

Overall, our synthetic strategy, which does not require the use of tin reagents, afforded enantiomerically pure (–)-**3** in a better overall yield (13%) without laborious procedures, compared to our previous synthetic route (2.4% total yield).[5]

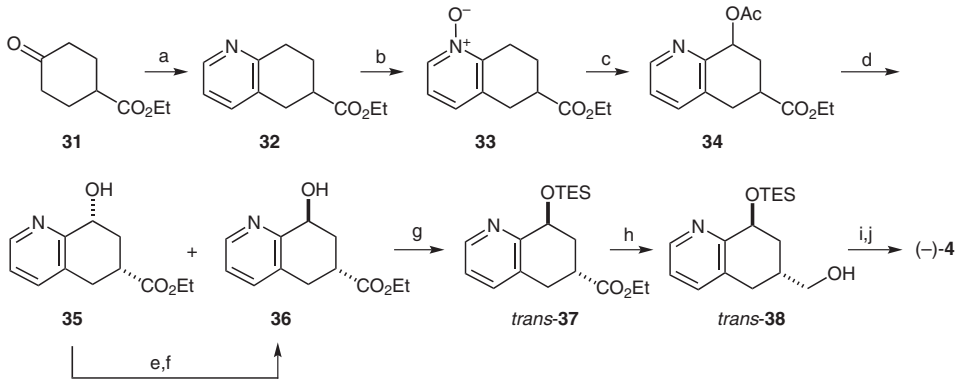
Along with (–)-**3**, six-membered intermediate (–)-**4** was also essential for our in vivo structure–activity relationship studies. As shown in Scheme 2, the previous synthetic route for (–)-**4** involved eleven reaction steps and required the use of a tin reagent.[5b] Under similar conditions as that for the highly diastereoselective reduction leading to (–)-**3** (Table 1, entry 7), diastereoselective reduction of the corresponding six-membered ketone **29** exhibited undesired *cis*-selectivity with a ratio of 85:15 (Scheme 7). Thus, we focused our efforts on the development of a convenient and short synthetic route to (–)-**4** that would not require the use of a tin reagent and would allow for scale-up to multigram quantities.

As shown in Scheme 8, the improved synthetic route for (–)-**4** involves the construction of a tetrahydroquinoline ring catalyzed by sodium tetrachloroaurate(III) as a key step. Based on the brilliant one-pot approach of Abbiati et al. for obtaining functional pyridines using various ketones and propargylamine,[14] commercially available ethyl 4-oxocyclohexanecarboxylate (**31**) was converted into tetrahydroquinoline **32**. Oxidation of **32** with 3-chloroperoxybenzoic acid afforded pyridine *N*-oxide **33**, which was heated with excess acetic anhydride to furnish 8-acetoxy analogue **34** as a mixture of *cis*- and *trans*-isomers. Cleavage of the acetyl group via treatment with sodium ethoxide in tetrahydrofuran–ethanol gave a mixture of the *cis*- and *trans*-isomers, **35** and **36**, in 1:2 ratio, which were separated using column chromatography. The stereochemistry of **35** and **36** were determined by NOE experiments. NOEs were observed between H_a and H_b, H_a and H_d, and H_b and H_d for **35**, and between H_a and H_c, H_a and H_d, and H_b and H_d for **36**. Furthermore, the large coupling constant (10.7 Hz) between H_a and H_c of **35** also supports this assignment (Figure 4). Fortunately, the undesired *cis*-isomer **35** was able to be transformed into the *trans*-isomer **36** in 73% yield via Mitsunobu reaction ($PhCO_2H$/Ph_3P/DIAD) followed by ethanolysis. The hydroxy group of *trans*-isomer **36** was protected by a triethylsilyl group to afford *trans*-**37** (28% total yield from ketone **31**). The ester group was reduced by lithium aluminum hydride to give alcohol *trans*-**38** as a racemic mixture, in which the enantiomers were separated by chiral HPLC to provide enantiomerically pure (–)-**38** (>99% ee). Finally, (–)-**38** was tosylated following typical procedures to yield key intermediate (–)-**4**. Our updated synthesis of (–)-**4** (13% total yield) reduced the total number of reaction steps to eight from eleven, avoided the use of any tin reagents, and allowed scale-up to >100-gram quantities.



Scheme 7 Reduction of six-membered ketone **30** by LS-Selectride

In summary, practical syntheses of enantiomerically pure (–)-**3** and (–)-**4**, as key intermediates of ORL1 antagonists, have been developed. Our new approaches do not require



Scheme 8 Synthesis of (–)-**4**. *Reagents and conditions*: (a) propargylamine, $NaAuCl_4$, EtOH, reflux; (b) MCPBA, $CHCl_3$, 0 °C to r.t.; (c) Ac_2O, 130 °C; (d) NaOEt, EtOH–THF, 0 °C; (e) benzoic acid, Ph_3P, DIAD, THF, 0 °C; (f) NaH, EtOH–THF, 0 °C, 73% (2 steps); (g) TESCl, Et_3N, DMAP, $CHCl_3$, r.t., 28% (5 steps from **31**); (h) $LiAlH_4$, THF, 0 °C, 98%; (i) Chiralpak AD column (*n*-hexane–*i*-PrOH, 50:1 with 0.1% Et_2NH); (j) TsCl, Et_3N, DMAP, $CHCl_3$, 50 °C, 48% (2 steps).

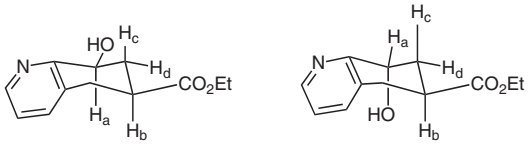


Figure 4 Plausible most stable conformations for compounds **35** and **36**

the use of any toxic tin reagents and allow for preparations in multigram-scale towards various kinds of pharmacological studies as well as structure–activity relationship studies for attenuating in vivo cardiovascular adverse effects.

All reagents and solvents were of commercial quality and were used without further purification unless otherwise noted. Melting points were determined using a Yanako MP micromelting point apparatus and are uncorrected. Optical rotations were determined on a Jasco P-1020 polarimeter. ^{1}H NMR spectra were recorded on a Varian MERCURYvx 400 spectrometer (400 MHz) or a JEOL AL-400 (400 MHz) spectrometer; TMS was used as an internal standard. ^{13}C NMR spectra were recorded on a JEOL AL-400 (100 MHz) spectrometer; $CDCl_3$ was used as internal standard (central line of a triplet at δ = 77.0). Mass spectra were recorded with electron-spray ionization (ESI) or electron-impact ionization (EI) on a micromass Quattro II, a micromass Q-Tof-2, or a JEOL-700V instrument. TLC was performed using E. Merck Kieselgel 60 F_{254} plates (0.25 mm). Silica gel column chromatography was performed using Wakogel C-300 or an appropriately sized pre-packed silica cartridge on a Biotage system. HPLC analysis of reaction mixtures was carried out using RP-HPLC (Zorbax Bonus RP 4.6 × 250 mm, s-3.5 μm) eluted with a linear gradient of 10–90% B–A over 25 min at a flow rate of 1.0 mL/min (solvent A: aq 10 mM potassium phosphate buffer, solvent B: MeOH).

(4*S*)-3-{(2*R*)-2-[(Benzyloxy)methyl]pent-4-enoyl}-4-isopropyloxazolidin-2-one [(+)-18]

(4*S*)-4-Isopropyl-3-(pent-4-enoyl)oxazolidin-2-one (**20**) was prepared according to the literature method.[6] To a soln of oxazolidinone **19** (108 g, 836 mmol) in THF (2.0 L) was added 2.66 M BuLi in hexane (345 mL, 918 mmol) at –78 °C, and the mixture was stirred at –78 °C for 30 min. Pent-4-enoyl chloride (102 mL, 924 mmol) was then added, and the resulting mixture was stirred at –78 °C for 30 min and then allowed to warm to –20 °C. The reaction was quenched by the addition of H_2O and the mixture was extracted with Et_2O (3 ×1.0 L). The combined Et_2O layers were then washed with sat. aq $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated by rotary evaporation to give crude **21** as an oil. To a stirred CH_2Cl_2 soln of crude **21** was added *i*-Pr_2NEt (160 mL, 918 mmol) and then 1.0 M $TiCl_4$ in CH_2Cl_2 (920 mL, 920 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, and $ClCH_2OBn$ (153 mL, 1.1 mol) was added keeping the internal temperature at 5–10 °C. The resulting mixture was stirred for 1.5 h at below 10 °C. To the mixture was added sat. aq NH_4Cl, and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (2 × 700 mL), and the combined organic layers were washed with sat. aq NH_4Cl and brine, dried (Na_2SO_4), and concentrated by rotary evaporation. The resulting crude **18** was used in the next step without further purification. Analytically pure **18** was obtained by column chromatography (silica gel, *n*-hexane–EtOAc, 20:1 to 1:1) as a colorless oil.

$[\alpha]_D^{20}$ +32.6 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (d, *J* = 7.3 Hz, 3 H), 0.87 (d, *J* = 7.3 Hz, 3 H), 2.26–2.37 (m, 2 H), 2.40–2.47 (m, 1 H), 3.64 (dd, *J* = 8.8, 4.9 Hz, 1 H), 3.75 (dd, *J* = 9.3, 7.3 Hz, 1 H), 4.17 (dd, *J* = 8.8, 3.0 Hz, 1 H), 4.24 (t, *J* = 8.8 Hz, 1 H), 4.28–4.35 (m, 1 H), 4.45–4.50 (m, 1 H), 4.47 (d, *J* = 12.2 Hz, 1 H), 4.52 (d, *J* = 12.2 Hz, 1 H), 5.02 (dd, *J* = 10.3, 1.0 Hz, 1 H), 5.07 (dd, *J* = 16.3, 1.5 Hz, 1 H), 5.76 (ddt, *J* = 16.3, 10.3, 7.4 Hz, 1 H), 7.26–7.34 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 17.8, 28.3, 33.0, 43.1, 58.4, 63.2, 70.9, 73.0, 117.1, 127.4, 127.5, 128.2, 135.0, 138.1, 153.8, 174.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{26}NO_4$: 332.1862; found: 332.1857.

Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 4.23; N, 7.60. Found: C, 68.76; H, 4.27; N, 7.69.

(2*R*)-2-[(Benzyloxy)methyl]pent-4-enoic Acid [(–)-21]

To a soln of THF (500 mL) and H_2O (500 mL) were added $LiOH·H_2O$ (70 g, 1.67 mol) and 30% H_2O_2 (330 mL) at 5 °C. To the mixture was slowly added a soln of the crude oxazolidinone **18** in THF (500 mL) keeping the internal temperature below 10 °C and the mixture was stirred at 5 °C for 2 h. The reaction was quenched by the addition of Na_2SO_3 (530 g) in H_2O and then $NaHCO_3$ (210 g) in H_2O. The THF was removed by rotary evaporation and the aqueous layer was washed with $CHCl_3$ (3 × 500 mL) and acidified by the addition of 6 M aq HCl. The aqueous mixture was then extracted with $CHCl_3$ (3 × 500 mL) and the combined organic layers were

washed with brine, dried ($MgSO_4$), and concentrated by rotary evaporation. This back-extraction procedure was repeated three times to give carboxylic acid **21** (158 g, 85% in 3 steps) as a colorless oil.

$[\alpha]_D^{26}$ –6.3 (*c* 1.00, $CHCl_3$).[15]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.27–2.34 (m, 1 H), 2.38–2.45 (m, 1 H), 2.73–2.80 (m, 1 H), 3.57 (dd, *J* = 9.2, 5.5 Hz, 1 H), 3.64 (dd, *J* = 9.2, 7.5 Hz, 1 H), 4.51 (s, 2 H), 5.01 (dd, *J* = 10.4, 1.0 Hz, 1 H), 5.05 (dd, *J* = 16.8, 1.4 Hz, 1 H), 5.72 (ddt, *J* = 16.8, 10.4, 7.4 Hz, 1 H), 7.23–7.34 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.6, 45.4, 69.6, 73.2, 117.5, 127.6, 127.7, 128.4, 134.5, 137.8, 179.3.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{16}O_3$: 220.1099; found: 220.1101.

Anal. Calcd for $C_{13}H_{16}O_3 \cdot 0.2H_2O$: C, 69.75; H, 7.38. Found: C, 69.87; H, 7.43.

(2*S*)-2-[(Benzyloxy)methyl]pent-4-en-1-ol [(–)-22]

To a stirred soln of **21** (157 g, 713 mmol) in DMF (1.5 L) was added CDI (140 g, 863 mmol) at 5 °C, and the mixture was stirred at 5 °C for 30 min. To the mixture was added a soln of $NaBH_4$ (54 g, 1.44 mol) in H_2O (250 mL) keeping the internal temperature below 20 °C. When the addition was complete, the reaction was quenched by the addition of sat. aq NH_4Cl. The mixture was then extracted with Et_2O (2 × 1.0 L). The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4), and concentrated by rotary evaporation to give alcohol **22** (114 g, 77%) as a colorless oil.

$[\alpha]_D^{26}$ –10.9 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94–2.01 (m, 1 H), 2.09 (dd, *J* = 8.3, 6.8 Hz, 2 H), 3.48 (dd, *J* = 8.4, 6.8 Hz, 1 H), 3.60 (dd, *J* = 8.4, 4.1 Hz, 1 H), 3.63 (dd, *J* = 10.7, 6.8 Hz, 1 H), 3.72 (dd, *J* = 10.7, 4.1 Hz, 1 H), 4.49 (d, *J* = 12.2 Hz, 1 H), 4.52 (d, *J* = 12.2 Hz, 1 H), 5.01 (dd, *J* = 10.3, 1.0 Hz, 1 H), 5.05 (dd, *J* = 17.1, 1.4 Hz, 1 H), 5.77 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1 H), 7.26–7.37 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.7, 40.4, 65.6, 73.2, 73.4, 116.5, 127.6, 127.7, 128.4, 136.2, 138.0.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{18}O_2$: 206.1307; found: 206.1315.

(2*R*)-2-[(Benzyloxy)methyl]-1-iodopent-4-ene [(–)-17]

To a stirred mixture of **22** (94.0 g, 456 mmol) and Et_3N (128 mL, 918 mmol) in THF (2.5 L) was slowly added MsCl (42.7 mL, 552 mmol), keeping the internal temperature below 10 °C, and the mixture was stirred for 30 min. The reaction was quenched by the addition of H_2O, and the volatiles were removed by rotary evaporation. The remaining aqueous mixture was extracted with Et_2O (3 × 700 mL). The combined organic layers were washed with H_2O (1 ×), 1 M aq HCl (2 ×), sat. aq $NaHCO_3$ (2 ×), and brine (1 ×), dried (Na_2SO_4), and concentrated by rotary evaporation. The crude product was dissolved in acetone (600 mL), and NaI (345 g, 2.30 mol) and $NaHCO_3$ (7.70 g, 91.7 mmol) were added to the mixture at r.t. The resulting mixture was stirred at r.t. for 2 d. The acetone was removed by rotary evaporation, and the mixture was partitioned with *n*-hexane–H_2O. The organic layer was then washed with H_2O and brine, dried (Na_2SO_4), and concentrated by rotary evaporation to give iodide **17** (134 g, 92%) as a colorless oil.

$[\alpha]_D^{26}$ –10.3 (*c* 2.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62–1.71 (m, 1 H), 2.07–2.21 (m, 2 H), 3.31 (dd, *J* = 9.8, 4.9 Hz, 1 H), 3.36 (dd, *J* = 9.3, 6.8 Hz, 1 H), 3.41 (dd, *J* = 9.8, 4.9 Hz, 1 H), 3.46 (dd, *J* = 9.3, 4.9 Hz, 1 H), 4.52 (s, 2 H), 5.08 (dd, *J* = 10.2, 1.4 Hz, 1 H), 5.13 (dd, *J* = 17.1, 1.5 Hz, 1 H), 5.73 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1 H), 7.28–7.34 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9, 35.7, 39.4, 72.3, 73.2, 117.4, 127.5, 127.6, 128.4, 135.1, 138.2.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{17}IO$: 316.0324; found: 316.0318.

Anal. Calcd for $C_{13}H_{17}IO$: C, 49.38; H, 5.42. Found: C, 49.59; H, 5.42.

3-{(3*R*)-3-[(Benzyloxy)methyl]hex-5-enyl}-2-bromopyridine [(–)-15]

To a stirred soln of 2,2,6,6-tetramethylpiperidine (32.0 mL, 190 mmol) in THF (200 mL) was added 2.44 M BuLi in *n*-hexane (78 mL, 190 mmol) at –70 °C, and the mixture was stirred at 0 °C for 30 min. To the resulting LTMP soln cooled to –78 °C were added DMPU (45.0 mL, 380 mmol) and 2-bromo-3-methylpyridine (32.7 g, 190 mmol), and the mixture was stirred below –65 °C for 30 min. To the mixture was added iodide **17** (30.0 g, 94.9 mmol) keeping the internal temperature below –65 °C. After completion of the addition, the mixture was warmed to –30 °C over 2 h. The reaction was quenched by the addition of H_2O and then EtOAc. The aqueous layer was extracted with EtOAc (2 × 800 mL), and the combined organic layers were washed with H_2O, sat. aq $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated by rotary evaporation. The residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 20:1 to 10:1) to give **15** (23.5 g, 69%) as a pale yellow oil.

$[\alpha]_D^{26}$ –0.64 (*c* 1.00, EtOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.61–1.77 (m, 2 H), 1.79–1.85 (m, 1 H), 2.14–2.27 (m, 2 H), 2.73 (t, *J* = 8.3 Hz, 2 H), 3.43 (dd, *J* = 9.3, 5.8 Hz, 1 H), 3.46 (dd, *J* = 9.3, 5.4 Hz, 1 H), 4.51 (s, 2 H), 5.02 (dd, *J* = 10.2, 1.4 Hz, 1 H), 5.06 (dd, *J* = 17.1, 1.5 Hz, 1 H), 5.78 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1 H), 7.17 (dd, *J* = 7.8, 4.4 Hz, 1 H), 7.27–7.35 (m, 5 H), 7.48 (dd, *J* = 7.8, 2.0 Hz, 1 H), 8.20 (dd, *J* = 4.4, 2.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.9, 32.7, 35.7, 38.1, 72.6, 73.2, 116.5, 122.8, 127.5, 127.6, 128.3, 136.4, 138.1, 138.5, 139.2, 144.3, 147.5.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{23}BrNO$: 360.0963; found: 316.0970.

Anal. Calcd for $C_{19}H_{22}BrNO$: C, 63.34; H, 6.15; N, 3.89. Found: C, 62.95; H, 6.28; N, 3.91.

(7*R*)-7-[(Benzyloxy)methyl]-9-methylene-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine [(–)-14]

To a soln of **15** (21.9 g, 60.8 mmol) and Et_3N (42 mL, 301 mmol) in DMF (1.2 L) were added $Pd(OAc)_2$ (1.40 g, 6.23 mmol) and dppp (3.80 g, 9.21 mmol). The mixture was stirred at 130 °C under an N_2 atmosphere for 14 h. The mixture was cooled to r.t. and diluted with Et_2O (1.0 L) and H_2O (2.0 L). The aqueous layer was extracted with Et_2O (2 × 1.0 L), and the combined organic layers were washed with H_2O (2 ×), sat. aq $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated by rotary evaporation. The residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 10:1 to 4:1) to give **14** (14.5 g, 85%) as a pale yellow oil.

$[\alpha]_D^{27}$ –13.8 (*c* 1.00, EtOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38–1.48 (m, 1 H), 1.98–2.05 (m, 1 H), 2.11–2.20 (m, 1 H), 2.28 (dd, *J* = 13.2, 9.4 Hz, 1 H), 2.71 (dd, *J* = 13.2, 3.4 Hz, 1 H), 2.74–2.86 (m, 2 H), 3.38 (dd, *J* = 9.3, 6.3 Hz, 1 H), 3.42 (dd, *J* = 9.3, 6.8 Hz, 1 H), 4.53 (s, 2 H), 5.26 (d, *J* = 1.0 Hz, 1 H), 5.58 (d, *J* = 2.0 Hz, 1 H), 7.07 (dd, *J* = 7.8, 4.9 Hz, 1 H), 7.26–7.36 (m, 5 H), 7.36 (dd, *J* = 7.8, 1.5 Hz, 1 H), 8.40 (dd, *J* = 4.9, 1.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.2, 32.1, 36.8, 40.4, 73.0, 74.2, 117.8, 121.9, 127.5, 127.6, 128.4, 135.1, 137.2, 138.5, 146.7, 147.9, 159.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}NO$: 280.1701; found; 280.1696.

Anal. Calcd for $C_{19}H_{21}NO{\cdot}0.15H_2O$: C, 80.88; H, 7.76; N, 5.07. Found: C, 80.90; H, 7.61; N, 4.97.

(7*R*)-7-[(*tert*-Butyldimethylsiloxy)methyl]-5,6,7,8-tetrahydro-9*H*-cyclohepta[*b*]pyridin-9-one [(–)-13]

Through a stirred soln of **14** (13.0 g, 46.5 mmol) in MeOH (500 mL) was bubbled with O_3/O_2 gas at –78 °C, and the mixture was gradually warmed to –50 °C over 1 h. With bubbling O_3, the mixture was stirred at –50 °C for an additional 8 h. The reaction was quenched by bubbling N_2 gas followed by addition of Me_2S (80 mL). The mixture was then warmed to r.t. and the volatiles were removed by rotary evaporation to give crude **24**. To the crude **24** were added MeOH (400 mL) and 1 M aq NaOH (50 mL), and the mixture was stirred at r.t. for 30 min. The MeOH was removed by rotary evaporation and the mixture was extracted with $CHCl_3$ (3 × 300 mL). The combined organic layers were washed with H_2O, 0.5 M aq NaOH, and brine, dried (Na_2SO_4), and concentrated by rotary evaporation. To a soln of the resulting residue in $CHCl_3$ (500 mL) were added imidazole (3.70 g, 54.3 mmol) and TBSCl (7.00 g, 46.4 mmol), and the mixture was stirred at r.t. for 3 h. The $CHCl_3$ was removed by rotary evaporation and the mixture was partitioned with EtOAc–H_2O. The organic layer was washed with H_2O, sat. aq $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated by rotary evaporation. The residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 4:1 to 1:1) to give **13** (10.4 g, 73%) as a colorless oil.

$[\alpha]_D^{27}$ –12.3 (*c* 1.00, EtOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 3 H), 0.05 (s, 3 H), 0.89 (s, 9 H), 1.70–1.77 (m, 1 H), 1.94–2.02 (m, 1 H), 2.07–2.14 (m, 1 H), 2.68 (dd, *J* = 15.6, 10.7 Hz, 1 H), 2.84–2.95 (m, 2 H), 3.00–3.07 (m, 1 H), 3.57 (dd, *J* = 6.3, 2.8 Hz, 2 H), 7.31 (dd, *J* = 7.8, 4.8 Hz, 1 H), 7.59 (d, *J* = 7.8 Hz, 1 H), 8.62 (d, *J* = 4.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.2, 18.6, 26.2, 28.8, 30.7, 36.5, 43.9, 66.9, 125.9, 137.5, 138.4, 148.6, 154.9, 203.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{28}NO_2Si$: 306.1889; found: 306.1892.

Anal. Calcd for $C_{17}H_{27}NO_2Si{\cdot}0.16H_2O$: C, 66.21; H, 8.93; N, 4.54. Found: C, 66.18; H, 8.84; N, 4.59.

(7*R*,9*S*)-7-[(*tert*-Butyldimethylsiloxy)methyl]-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-ol (25)

To a stirred soln of **14** (5.35 g, 17.5 mmol) in THF (150 mL) was added 1.0 M LS-Selectride in THF (35.0 mL) at –78 °C, and the mixture was stirred at –78 °C for 1 h. The reaction was quenched by the addition of H_2O (15 mL) and EtOH (30 mL) and the mixture was warmed to r.t. over 1 h. 1 M aq NaOH (50 mL) and 30% aq H_2O_2 (75 mL) were added to the mixture at 0 °C, and the mixture was then stirred at 40 °C for 30 min. The mixture was diluted with EtOAc (200 mL), and the aqueous layer was extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated by rotary evaporation. The residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 20:1 to 1:2) to give **25** (4.23 g, 79%) as a colorless solid; mp 53.5–54.3 °C.

$[\alpha]_D^{27}$ –32.4 (*c* 1.00, EtOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.08 (s, 6 H), 0.91 (s, 9 H), 1.63 (ddt, *J* = 14.6, 10.7, 3.9 Hz, 1 H), 1.75 (ddd, *J* = 13.6, 10.2, 4.4 Hz, 1 H), 1.82–1.90 (m, 1 H), 1.99–2.04 (m, 1 H), 2.07–2.13 (m, 1 H), 2.68 (ddd, *J* = 14.6, 6.8, 3.0 Hz, 1 H), 2.88 (ddd, *J* = 17.1, 10.7, 2.9 Hz, 1 H), 3.73 (dd, *J* = 10.2, 6.8 Hz, 1 H), 3.78 (dd, *J* = 10.2, 7.8 Hz, 1 H), 4.93 (dd, *J* = 10.2, 2.9 Hz, 1 H), 7.12 (dd, *J* = 7.3, 4.8 Hz, 1 H), 7.43 (d, *J* = 7.3 Hz, 1 H), 8.34 (d, *J* = 4.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.0, 18.6, 26.2, 27.7, 29.4, 37.2, 37.9, 65.8, 68.9, 122.6, 135.6, 137.4, 145.1, 160.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{30}NO_2Si$: 308.2046; found: 308.2039.

Anal. Calcd for $C_{17}H_{29}NO_2Si$: C, 66.40; H, 9.51; N, 4.55. Found: C, 66.00; H, 9.32; N, 4.30.

Reduction of Ketone 13 with Tributyltin Hydride (Table 1, Entries 1–3)

To a stirred soln of **13** in toluene (0.1 M) or toluene–EtOH (1:3, 0.1 M) were added Bu_3SnH (3 equiv) and V-40 (0.3 equiv) or AIBN (0.3 equiv) at r.t., and the resulting mixture was heated. Completion of the reaction was detected by TLC. For entry 1, the mixture was concentrated, and the residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 10:1 to 1:2). For entries 2 and 3, the mixture was analyzed by RP-HPLC [(Zorbax Bonus RP 4.6 × 250 mm, s-3.5 μm) t_R = 18.0 (**25**), 16.8 min (**26**)].

(7*R*,9*S*)-7-(Hydroxymethyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-ol [(–)-27]

To a stirred soln of **25** (7.16 g, 23.3 mmol) in THF (80 mL) was added 0.5 M aq HCl (40 mL) at r.t., and the mixture was stirred at r.t. for 1 h. The THF was removed by rotary evaporation, K_2CO_3 (5.0 g) was added to the mixture, and the resulting mixture was extracted with $CHCl_3$–*i*-PrOH (5:1, 5 × 500 mL). The combined organic layers were dried ($MgSO_4$) and concentrated by rotary evaporation. The resulting solid was washed with *i*-Pr_2O to afford **27** (4.14 g, 92%); 90% ee {HPLC (Chiralpak AD, 0.46 cm × 25 cm, *n*-hexane–EtOH, 9:1 with 0.1% Et_2NH, flow rate = 1.0 mL/min): t_R = 17.9 [(–)-**27**], 21.8 min [(+)-**27**]}. **27** (3.56 g, 21.4 mmol) was recrystallized (*i*-Pr_2O–MeOH, 10:1, 100 mL) to give enantiomerically pure (–)-**27** (2.63 g, 74%) as colorless crystals; mp 135–136 °C.

$[\alpha]_D^{27}$ –54.4 (*c* 1.00, EtOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66–1.86 (m, 3 H), 1.98 (br s, 1 H), 2.03–2.16 (m, 2 H), 2.73 (ddd, *J* = 14.6, 6.8, 3.4 Hz, 1 H), 2.87 (ddd, *J* = 14.6, 11.2, 3.4 Hz, 1 H), 3.79 (dd, *J* = 10.7, 7.3 Hz, 1 H), 3.83 (dd, *J* = 10.7, 6.3 Hz, 1 H), 4.95 (dd, *J* = 10.2, 2.9 Hz, 1 H), 5.38 (br s, 1 H), 7.13 (dd, *J* = 7.3, 4.9 Hz, 1 H), 7.44 (dd, *J* = 7.3, 1.5 Hz, 1 H), 8.35 (dd, *J* = 4.9, 1.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.6, 29.1, 36.6, 37.7, 65.2, 68.6, 122.4, 135.1, 137.2, 144.9, 160.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{16}NO_2$: 194.1181; found: 194.1184.

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.32; H, 7.84; N, 7.12.

[(7*R*,9*S*)-9-(*tert*-Butyldimethylsiloxy)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-7-yl]methanol [(–)-28]

To a stirred soln of **27** (4.49 g, 23.3 mmol) in DMF (100 mL) were added imidazole (7.90 g, 116 mmol) and TBSCl (10.7 g, 71.0 mmol) at r.t., and the mixture was stirred at r.t. for 4 h. The mixture was partitioned with EtOAc and H_2O, and the organic layer was separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with H_2O and brine, dried (Na_2SO_4), and concentrated by rotary evaporation. To a stirred soln of the residue in THF (200 mL) was added 0.5 M aq HCl (100 mL), and the mixture was stirred at r.t. for 1 h. The mixture was neutralized by the addition of sat. aq $NaHCO_3$. The THF was removed by rotary evaporation, and the resulting mixture was extracted with EtOAc (2 × 100 mL). The organic layer was washed with H_2O and brine, dried (Na_2SO_4), and concentrated by rotary evaporation. The residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 4:1 to 1:2) to give **28** (6.90 g, 96%) as a colorless oil.

$[\alpha]_D^{27}$ –50.1 (*c* 1.00, EtOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.24 (s, 3 H), 0.08 (s, 3 H), 0.85 (s, 9 H), 1.13 (tdd, *J* = 13.0, 12.5, 1.4 Hz, 1 H), 1.43 (ddd, *J* = 14.0, 12.5, 1.4 Hz, 2 H), 2.09–2.17 (m, 2 H), 2.44–2.54 (m, 1 H), 2.58 (ddd, *J* = 14.0, 7.0, 1.3 Hz, 1 H), 3.39 (t, *J* = 12.5 Hz, 1 H), 3.42–3.57 (m, 2 H), 5.10 (d, *J* = 6.8 Hz, 1 H), 7.07 (dd, *J* = 7.3, 4.9 Hz, 1 H), 7.39 (dd, *J* = 7.3, 1.5 Hz, 1 H), 8.28 (dd, *J* = 4.9, 1.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3, –5.0, 18.1, 25.8, 31.1, 32.2, 35.9, 38.5, 68.9, 77.5, 122.4, 137.5, 138.1, 145.4, 162.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{30}NO_2Si$: 308.2046; found: 308.2044.

[(7*R*,9*S*)-9-(*tert*-Butyldimethylsiloxy)-7-[(tosyloxy)methyl]-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine [(–)-3]

To a stirred soln of **28** (6.90 g, 22.4 mmol) in $CHCl_3$ (150 mL) were added Et_3N (9.40 mL, 67.4 mmol), DMAP (270 mg, 2.21 mmol), and TsCl (8.54 g, 44.8 mmol) at r.t. The mixture was stirred at 50 °C for 2.5 h and then cooled to r.t. and diluted with Et_2O (600 mL) and H_2O. The organic layer was separated, washed with sat. aq $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated by rotary evaporation. The residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 10:1 to 4:1) to give (–)-**3** (10.2 g, 99%) as a colorless solid; >99% ee {HPLC (Chiralcel OD, 0.46 cm × 25 cm, *n*-hexane–*i*-PrOH, 95:5 with 0.1% Et_2NH, flow rate = 1.0 mL/min): t_R = 6.2 [(+)-**3**], 10.0 min [(–)-**3**]}; mp 38.8–39.2 °C.

$[\alpha]_D^{27}$ –43.6 (*c* 0.50, DMF).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.27 (s, 3 H), 0.04 (s, 3 H), 0.82 (s, 9 H), 1.15 (td, *J* = 13.0, 12.5 Hz, 1 H), 1.43 (dd, *J* = 13.2, 12.5, Hz, 1 H), 1.95–2.04 (m, 2 H), 2.45 (s, 3 H), 2.53 (dd, *J* = 13.2, 6.3 Hz, 1 H), 2.64–2.67 (m, 1 H), 3.32 (t, *J* = 13.2 Hz, 1 H), 3.84 (dd, *J* = 9.3, 6.3 Hz, 1 H), 3.91 (dd, *J* = 9.3, 5.4 Hz, 1 H), 5.04 (d, *J* = 6.8 Hz, 1 H), 7.06 (dd, *J* = 7.3, 4.9 Hz, 1 H), 7.34 (d, *J* = 8.3 Hz, 2 H), 7.36 (dd, *J* = 7.3, 1.5 Hz, 1 H), 7.77 (d, *J* = 8.3 Hz, 2 H), 8.27 (dd, *J* = 4.9, 1.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3, –5.0, 18.0, 21.6, 25.8, 30.7, 31.7, 35.4, 35.5, 75.8, 77.1, 122.6, 127.9, 129.8, 133.0, 137.5, 137.6, 144.7, 145.6, 161.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{36}NO_4SiS$: 462.2134; found: 462.2135.

Anal. Calcd for $C_{24}H_{35}NO_4SiS$: C, 62.44; H, 7.64; N, 3.03. Found: C, 62.32; H, 7.53; N, 2.83.

Ethyl 5,6,7,8-Tetrahydroquinoline-6-carboxylate (32)

To a stirred soln of propargylamine (324 g, 5.88 mol) and $NaAuCl_4 \cdot 2H_2O$ (29.2 g, 73.4 mmol) in EtOH (2.5 L) was added a soln of ethyl 4-oxocyclohexanecarboxylate (**31**, 500 g, 2.94 mol) in EtOH (250 mL) at 60 °C. The mixture was stirred at reflux temperature overnight and then cooled to r.t. and filtered through a pad of Celite; the filtrate was concentrated by rotary evaporation. The residue was used in the next step without further purification. Analytically pure **32** was obtained by column chromatography (silica gel, *n*-hexane–EtOAc, 20:1 to 1:1) as a pale brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.0 Hz, 3 H), 1.89–2.01 (m, 1 H), 2.23–2.33 (m, 1 H), 2.69–2.76 (m, 1 H), 2.89–3.05 (m, 4 H), 4.15 (q, *J* = 7.0 Hz, 2 H), 7.02 (dd, *J* = 7.4, 4.7 Hz, 1 H), 7.36 (dd, *J* = 7.4, 0.8 Hz, 1 H), 8.34 (dd, *J* = 4.7, 0.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 25.7, 30.8, 31.3, 39.4, 60.6, 121.2, 130.2, 136.8, 147.2, 156.0, 174.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}NO_2$: 206.1181; found: 206.1178.

Anal. Calcd for $C_{12}H_{15}NO_2 \cdot 0.33H_2O$: C, 68.24; H, 7.47; N, 6.63. Found: C, 68.18; H, 7.65; N, 6.80.

Ethyl *cis*-8-Hydroxy-5,6,7,8-tetrahydroquinoline-6-carboxylate (35) and Ethyl *trans*-8-Hydroxy-5,6,7,8-tetrahydroquinoline-6-carboxylate (36)

To a stirred soln of the crude **32** in $CHCl_3$ (4.5 L) was added MCPBA (869 g, ca. 65% purity) at 0 °C. The mixture was stirred at r.t. for 2.5 h, MCPBA (174 g) was added again, and the mixture was stirred for an additional 30 min. The reaction was quenched by the addition of sat. aq $NaHCO_3$, and the mixture was extracted with $CHCl_3$ (1 L). The combined organic layers were washed with sat. aq $NaHCO_3$, 10% aq Na_2SO_3, and brine, dried (Na_2SO_4), and concentrated by rotary evaporation to give crude *N*-oxide **33**. The residue was dissolved in Ac_2O (2.0 L), and the resulting mixture was stirred at 130 °C for 1 h. Ac_2O was removed by rotary evaporation, and the residue was partitioned with sat. aq $NaHCO_3$ and $CHCl_3$ (1 L). The aqueous layer was extracted with $CHCl_3$ (1 L), and the combined organic layers were washed with sat. aq $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated by rotary evaporation to afford crude **34** as a mixture of *cis*- and *trans*-isomers. To a soln of crude **34** in THF (3.0 L) cooled at 0 °C was added an EtOH soln of NaOEt [prepared from Na (77.2 g, 3.36 mol) and EtOH (3.4 L)]. The mixture was stirred at 0 °C for 30 min, and the reaction was quenched by the addition of sat. aq NH_4Cl. The soln was concentrated by rotary evaporation, and the resulting mixture was partitioned with H_2O and $CHCl_3$ (1.5 L). The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (2 × 1.5 L). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated by rotary evaporation. The residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 2:1 to 0:10) to give *cis*-isomer **35** (91.1 g, 14%) from a less polar fraction and *trans*-isomer **36** (336 g) from a polar fraction including some impurities, which was used in the next step without further purification.

***cis*-Isomer 35**

Colorless crystals; mp 90.3–91.0 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.3 Hz, 3 H), 1.89 (td, *J* = 12.2, 10.9 Hz, 1 H), 2.70 (ddd, *J* = 12.2, 5.9, 1.5 Hz, 1 H), 2.87–2.96 (m, 1 H), 3.02–3.15 (m, 2 H), 4.21 (q, *J* = 7.3 Hz, 2 H), 4.78 (dd, *J* = 10.7, 5.4 Hz, 1 H), 7.17 (dd, *J* = 7.8, 4.9 Hz, 1 H), 7.47 (dd, *J* = 7.8, 1.5 Hz, 1 H), 8.44 (dd, *J* = 4.9, 1.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 30.5, 33.4, 37.6, 60.9, 68.7, 122.6, 129.3, 136.9, 147.0, 157.0, 174.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}NO_3$: 222.1130; found: 222.1134.

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.12; H, 6.79; N, 6.19.

***trans*-Isomer 36**

Analytically pure **36** was obtained by crystallization (*i*-Pr_2O) as colorless needles; mp 106–107 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.3 Hz, 3 H), 2.20 (ddd, *J* = 14.1, 9.8, 4.4 Hz, 1 H), 2.40 (dt, *J* = 14.1, 3.8 Hz, 1 H), 3.00–3.06 (m, 2 H), 3.08–3.17 (m, 1 H), 4.19 (q, *J* = 7.3 Hz, 2 H), 4.41 (br s, 1 H), 4.87 (t, *J* = 4.4 Hz, 1 H), 7.17 (dd, *J* = 7.8, 4.9 Hz, 1 H), 7.50 (dd, *J* = 7.8, 1.5 Hz, 1 H), 8.42 (dd, *J* = 4.9, 1.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 30.6, 33.1, 35.1, 60.8, 67.0, 122.9, 130.2, 137.3, 147.4, 156.6, 174.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}NO_3$: 222.1130; found: 222.1129.

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.07; H, 6.78; N, 6.17. Found: C, 65.12; H, 6.79; N, 6.19.

Ethyl *trans*-8-Hydroxy-5,6,7,8-tetrahydroquinoline-6-carboxylate (36) by Mitsunobu Reaction and Subsequent Alcoholysis

To a stirred soln of **35** (240 mg, 1.08 mmol) in THF (10 mL) were

subsequently added Ph_3P (341 mg, 1.30 mmol), $PhCO_2H$ (159 mg, 1.30 mmol), and DIAD (256 μL, 1.30 mmol) at 0 °C, and the mixture was stirred at 0 °C for 6 h. Volatiles were removed by rotary evaporation, and the residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 10:1 to 1:1) to give the corresponding benzoate (577 mg) with some impurities. NaH (60% in mineral oil, 52.1 mg) was added to a stirred mixture of the crude product in THF (10 mL)–EtOH (2 mL) at 0 °C, and the mixture was stirred at 0 °C for 15 min. The reaction was quenched by the addition of sat. aq NH_4Cl, and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated by rotary evaporation. The residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 3:1 to 0:10) to give **36** (174 mg, 73% in 2 steps).

Ethyl 8-(Triethylsiloxy)-5,6,7,8-tetrahydroquinoline-6-carboxylate (*trans*-37)

To a stirred soln of crude **36** (336 g) in $CHCl_3$ (5.0 L) were added DMAP (18.6 g, 152 mmol), Et_3N (634 mL, 4.55 mol), and TESCl (510 mL, 3.00 mol) at 0 °C, and the mixture was stirred at 0 °C for 3 h. H_2O (2 L) and $CHCl_3$ were added to the mixture, and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (2 × 1 L), and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated by rotary evaporation. The residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 20:1 to 4:1) to give *trans*-**37** (276 g, 28% in 5 steps) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.66 (q, *J* = 7.8 Hz, 6 H), 0.94 (t, *J* = 7.8 Hz, 9 H), 1.29 (t, *J* = 7.3 Hz, 3 H), 1.93 (td, *J* = 13.4, 2.9 Hz, 1 H), 2.38 (dtd, *J* = 13.4, 2.9, 1.7 Hz, 1 H), 2.94 (dd, *J* = 17.1, 11.7 Hz, 1 H), 3.09 (dd, *J* = 17.1, 5.7 Hz, 1 H), 3.29 (tdd, *J* = 12.2, 5.7, 2.8 Hz, 1 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 4.88 (t, *J* = 2.9 Hz, 1 H), 7.13 (dd, *J* = 7.8, 4.9 Hz, 1 H), 7.43 (dd, *J* = 7.8, 1.5 Hz, 1 H), 8.43 (dd, *J* = 4.9, 1.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 5.0, 6.7, 14.2, 30.4, 34.1, 34.9, 60.6, 69.2, 122.8, 130.1, 137.0, 147.3, 156.1, 175.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{30}NO_3Si$: 336.1995; found 336.1991.

[(6*RS*,8*SR*)-8-(Triethylsiloxy)-5,6,7,8-tetrahydroquinolin-6-yl]methanol (*trans*-38)

To a stirred suspension of $LiAlH_4$ (25.0 g, 659 mmol) in THF (3.0 L) was added a soln of *trans*-**37** (276 g, 823 mmol) in THF (300 mL) keeping the internal temperature below 15 °C; the mixture was then stirred at 0 °C for 30 min. The reaction was quenched by the subsequent addition of H_2O (25 mL), 1 M aq NaOH (25 mL), and H_2O (75 mL). The mixture was filtered through a pad of Celite, and the filtrate was concentrated by rotary evaporation to remove THF. The resulting mixture was extracted with $CHCl_3$ (3 × 2 L), and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated by rotary evaporation. The residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 17:3 to 4:1) to give *trans*-**38** (236 g, 98%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.65 (q, *J* = 7.8 Hz, 6 H), 0.93 (t, *J* = 7.8 Hz, 9 H), 1.56–1.66 (m, 1 H), 2.09 (ddd, *J* = 13.7, 3.9, 1.5 Hz, 1 H), 2.47–2.56 (m, 2 H), 2.96 (d, *J* = 11.7 Hz, 1 H), 3.62–3.74 (m, 2 H), 4.89 (t, *J* = 2.9 Hz, 1 H), 7.11 (dd, *J* = 7.8, 4.4 Hz, 1 H), 7.42 (dd, *J* = 7.8, 1.0 Hz, 1 H), 8.42 (dd, *J* = 4.4, 1.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 5.1, 6.8, 30.9, 31.5, 35.1, 67.7, 69.7, 122.6, 131.3, 137.1, 147.2, 156.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{28}NO_2Si$: 294.1889; found: 294.1887.

Anal. Calcd for $C_{16}H_{27}NO_2Si·0.15H_2O$: C, 64.88; H, 9.29; N, 4.73. Found: C, 64.87; H, 9.28; N, 4.98.

[(6*R*,8*S*)-8-(Triethylsiloxy)-5,6,7,8-tetrahydroquinolin-6-yl]methanol [(–)-38] by Chiral Separation of *trans*-38

Racemic *trans*-**38** (195 g) was resolved using chiral HPLC (Chiralcel AD, 5 cm × 50 cm, *n*-hexane–*i*-PrOH, 50:1 with 0.1% Et_2NH, flow rate = 100 mL/min) to give enantiomerically pure (–)-**38** from a faster fraction (93.3 g) with >99% ee [HPLC (Chiralcel AD, 0.46 cm × 25 cm, *n*-hexane–*i*-PrOH, 50:1 with 0.1% Et_2NH, flow rate = 1.0 mL/min): t_R = 12.5 min (–)-**38**, 16.2 min (+)-**38**].

$[\alpha]_D^{27}$ –44.7 (*c* 1.00, EtOH).

(6*R*,8*S*)-6-[(Tosyloxy)methyl]-8-(triethylsiloxy)-5,6,7,8-tetrahydroquinoline [(–)-4]

To a stirred soln of (–)-**38** (90.9 g, 310 mmol) in $CHCl_3$ (800 mL) were added DMAP (3.78 g, 31.0 mmol), Et_3N (103 mL, 739 mmol), and TsCl (70.9 g, 372 mmol) at 0 °C, and the mixture was stirred at 50 °C for 1.5 h. Et_3N (43.1 mL, 310 mmol) and TsCl (29.5 g, 155 mmol) were then added to the mixture two times in every 30 min, and the resulting mixture was stirred for an additional 1 h. The mixture was cooled to r.t., washed with H_2O, sat. aq $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated by rotary evaporation. The residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 10:0 to 1:1) to give (–)-**4** (128 g, 92%) as a pale yellow oil.

$[\alpha]_D^{28}$ –32.6 (*c* 8.59, EtOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.60 (q, *J* = 7.8 Hz, 6 H), 0.88 (t, *J* = 7.8 Hz, 9 H), 1.60 (td, *J* = 13.2, 2.9 Hz, 1 H), 1.94 (ddd, *J* = 13.2, 4.4, 2.9 Hz, 1 H), 2.46 (s, 3 H), 2.51 (dd, *J* = 16.1, 11.2 Hz, 1 H), 2.62–2.73 (m, 1 H), 2.89 (dd, *J* = 16.1, 5.1 Hz, 1 H), 4.02 (dd, *J* = 9.5, 6.6 Hz, 1 H), 4.10 (dd, *J* = 9.5, 5.1 Hz, 1 H),), 4.83 (t, *J* = 2.9 Hz, 1 H), 7.10 (dd, *J* = 7.8, 4.4 Hz, 1 H), 7.36 (d, *J* = 8.3 Hz, 2 H), 7.37 (d, *J* = 7.8 Hz, 1 H), 7.82 (d, *J* = 8.3 Hz, 2 H), 8.41 (d, *J* = 4.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 5.0, 6.8, 21.6, 28.2, 30.9, 34.7, 69.3, 74.3, 122.7, 127.9, 129.8, 130.2, 133.0, 137.0, 144.8, 147.4, 156.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{34}NO_4SiS$: 448.1975; found: 448.1975.

Anal. Calcd for $C_{23}H_{33}NO_4SiS·0.2H_2O$: C, 61.22; H, 7.46; N, 3.10. Found: C, 61.06; H, 7.53; N, 2.98.

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References

(1) (a) Mollereau, C.; Parmentier, M.; Mailleux, P.; Butour, J.; Moisand, C.; Chalon, P.; Caput, D.; Vassart, G.; Meunier, J.-C. *FEBS Lett.* **1994**, *341*, 33. (b) Fukuda, K.; Kato, S.; Mori, K.; Nishi, M.; Takeshima, H.; Iwabe, N.; Miyata, T.; Houtani, T.; Sugimoto, T. *FEBS Lett.* **1994**, *343*, 42. (c) Chen, Y.; Fan, Y.; Liu, J.; Mestek, A.; Tian, M.; Kozak, C. A.; Yu, L. *FEBS Lett.* **1994**, *347*, 279. (d) Pan, Y.-X.; Cheng, J.; Xu, J.; Rossi, G.; Jacobson, E.; Ryan-Moro, J.; Brooks, A. I.; Dean, G. E.; Standifer, K. M.; Pasternak, G. W. *Mol. Pharmacol.* **1995**, *47*, 1180. (e) Reinsceid, R. K.; Nothacker, H.-P.; Bourson, A.; Ardati, A.; Henningsen, R. A.; Bunzow, J. R.; Grady, D. K.; Langen, H.; Monsma, F. J. Jr.; Civelli, O. *Science* **1995**, *270*, 792. (f) Meunier, J.-C.; Mollereau, C.; Toll, L.; Suaudeu, C.; Moisand, C.; Alvinerie, P.; Butour, J.-L.; Guillemot, J.-C.; Ferrara, P.;

Monsarrat, B.; Mazarguil, H.; Vassart, G.; Parmentier, M.; Constentin, J. *Nature* **1995**, *377*, 532.

(2) (a) Mogil, J. S.; Grisel, J. E.; Reinscheid, R. K.; Civelli, O.; Belknap, J. K.; Grandy, D. K. *Neuroscience* **1996**, *75*, 333. (b) Manabe, T.; Noda, Y.; Mamiya, T.; Katagiri, H.; Houtani, T.; Nishi, M.; Noda, T.; Takahashi, T.; Sugimoto, T.; Nabeshima, T.; Takeshima, H. *Nature (London)* **1998**, *394*, 577. (c) Jenck, F.; Moreau, J.-L.; Martin, J. R.; Kilpatrick, G. J.; Reinscheid, R. K.; Monsma, F. J. Jr.; Nothacker, H.-P.; Civelli, O. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 14854. (d) Champion, H. C.; Katwitz, P. J. *Life Sci.* **1997**, *60*, 241. (e) Gumusel, B.; Hao, Q.; Hyman, A.; Chang, J.-K.; Kapusta, D. R.; Lippton, H. *Life Sci.* **1997**, *60*, 141.

(3) Reviews: (a) Chiou, L.-C.; Liao, Y.-Y.; Fan, P.-C.; Kuo, P.-H.; Wang, C.-H.; Riemer, C.; Prinssen, E. P. *Curr. Drug Targets* **2007**, *8*, 117. (b) Bignan, G. C.; Connolly, P. J.; Middleton, S. *Expert Opin. Ther. Patents* **2005**, *15*, 357. (c) Zaveri, N. *Life Sci.* **2003**, *73*, 663. (d) Ronzoni, S.; Peretto, I.; Giardina, G. A. M. *Expert Opin. Ther. Patents* **2001**, *11*, 525.

(4) Yoshizumi, T.; Takahashi, H.; Miyazoe, H.; Sugimoto, Y.; Tsujita, T.; Kato, T.; Ito, H.; Kawamoto, H.; Hirayama, M.; Ichikawa, D.; Azuma-Kanoh, T.; Ozaki, S.; Shibata, Y.; Tani, T.; Chiba, M.; Ishii, Y.; Okuda, S.; Tadano, K.; Fukuroda, T.; Okamoto, O.; Ohta, H. *J. Med. Chem.* **2008**, *51*, 4021.

(5) (a) Yoshizumi, T.; Miyazoe, H.; Sugimoto, Y.; Takahashi, H.; Okamoto, O. *Synthesis* **2005**, 1593. (b) Takahashi, H.; Sugimoto, Y.; Yoshizumi, T.; Kato, T.; Asai, M.; Miyazoe, H. WO 2005085228, **2005**.

(6) Faull, A. W.; Brewster, A. G.; Brown, G. R.; Smithers, M. J.; Jackson, R. *J. Med. Chem.* **1995**, *38*, 686.

(7) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215.

(8) ^{1}H NMR and RP-HPLC analyses of the reaction mixture indicated that the diastereoselectivity was >99:1.

(9) Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 260.

(10) (a) Shorey, B. J.; Lee, V.; Baldwin, J. E. *Tetrahedron* **2007**, *63*, 5587. (b) Kiehne, U.; Bunzen, J.; Lützen, A. *Synthesis* **2007**, 1061. (c) Kaiser, E. M.; Petty, J. D. *Synthesis* **1975**, 705.

(11) Reviews: (a) Tsuji, J. *Palladium Reagent and Catalysts. Innovation in Organic Synthesis*; John Wiley: New York, **1995**. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (c) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379.

(12) Shibata, I.; Baba, A. *Curr. Org. Chem.* **2002**, *6*, 665.

(13) The most stable conformer was investigated at the B3LYP/6-31G* level. All calculations were performed with the package SPARTAN' 06 (Wavefunction, Inc. Irvine, CA).

(14) Abbiati, G.; Arcadi, A.; Bianchi, G.; Giuseppe, S. D.; Marinelli, F.; Rossi, E. *J. Org. Chem.* **2003**, *68*, 6959.

(15) This levorotatory optical rotation for the (*R*)-isomer {$[\alpha]_D^{26}$ –6.3 (*c* 1.00, $CHCl_3$)} was not in agreement with the reported data for the (*S*)-isomer {$[\alpha]_D$ –24.4 (*c* 2.67, $CHCl_3$)}.[16] However, the levorotatory optical rotation of the corresponding ester, methyl (2*R*)-2-[(benzyloxy)methyl]pent-4-enoate {$[\alpha]_D^{24}$ –5.9 (*c* 4.0, $CHCl_3$)}, which we prepared from (*R*)-**21**, was reasonable, compared to the dextrorotatory optical rotation of the (*S*)-isomer {$[\alpha]_D$ +3.2 (*c* 4.0, $CHCl_3$)}.[16]

(16) Sime, J. T.; Barnes, R. D.; Elson, S. W.; Jarvest, R. L.; O'Toole, K. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1653; although (*S*)-enriched samples, {$[\alpha]_D$ –24.4 (*c* 2.67, $CHCl_3$)} of **21** and {$[\alpha]_D$ +3.2 (*c* 4.0, $CHCl_3$)} of methyl 2-[(benzyloxy)methyl]pent-4-enoate, were prepared, the ee values were not reported.