A Novel Route to 6-Substituted Piperidin-3-ols via Domino Cyclization of 2-Hydroxy-6-phosphinyl-5-hexenyl Tosylates with Primary Amines: Synthesis of (±)-Pseudoconhydrine and (±)-*epi*-Pseudoconhydrine

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Abstract: 2-Hydroxy-6-phosphinyl-5-hexenyl tosylates, oxirane ring-opening products derived from glycidyl tosylates and phosphinyl-substituted allyl anions, undergo domino S_N2–Michael reactions with primary amines to give 6-phosphinylmethylpiperidin-3-ols. The phosphinyl unit can be used in Horner olefination reactions. This approach is applied to the synthesis of racemic pseudoconhydrine and its epimer.

Key words: phosphine oxides, domino reactions, cyclization, piperidines, Horner olefination

The piperidine ring represents an important structural motif in natural products making the synthesis of this heterocycle the subject of continuing research.[1–3] In particular, substituted 3(5)-hydroxypiperidine units are present in many alkaloids showing a broad spectrum of biological and pharmacological properties.[4,5] Typical examples include cassine (**1**),[6] prosophylline (**2**),[7] 1-deoxyaltronojirimycin (**3**),[8] (–)-5-hydroxysedamine (**4**),[9] and pseudoconhydrine (**5**)[10] (Figure 1). The 3-hydroxypiperidine **5** is a well-known alkaloid first isolated in 1891 from poison hemlock (*Conium maculatum*), along with four other alkaloids.[10] Various syntheses of racemic[11] and of enantiomerically pure[12] pseudoconhydrine have been reported. In the early syntheses, the substituted piperidine was obtained by hydrogenation of the corresponding pyridine,[11a–c,12e] but methods in which the piperidine ring is elaborated indirectly into the target molecule also rely on the parent pyridine.[11e–g,i,k] In asymmetric syntheses, the piperidine ring is often formed by an S_N reaction[11j,12a,b,d,f,g,l] or by a cyclocondensation between an amine unit and a carbonyl group.[11d,12c,h,k,n,q] Important methods include ring enlargement of pyrrolidines,[11h,12i] (cyclo)addition methods,[12j,m,r] a metathesis reaction,[12o] and hydroformylation.[12p] If the source of the ring nitrogen in the target molecule is not a pyridine nitrogen, then the synthetic methodology often requires that the ring nitrogen be introduced in a higher oxidation state (nitro,[11d] hydroxylamine,[11h,12h] nitroso,[12c] or azide[12d,f,j]), or indirectly as a nitrile group.[11j] We herein report a synthesis of 3-hydroxypiperidines in which the ring closure occurs in a domino fashion and where the ring nitrogen is supplied conveniently by a primary amine. In addition, a phosphinyl moiety offers a handle for subsequent olefination chemistry (Scheme 1).

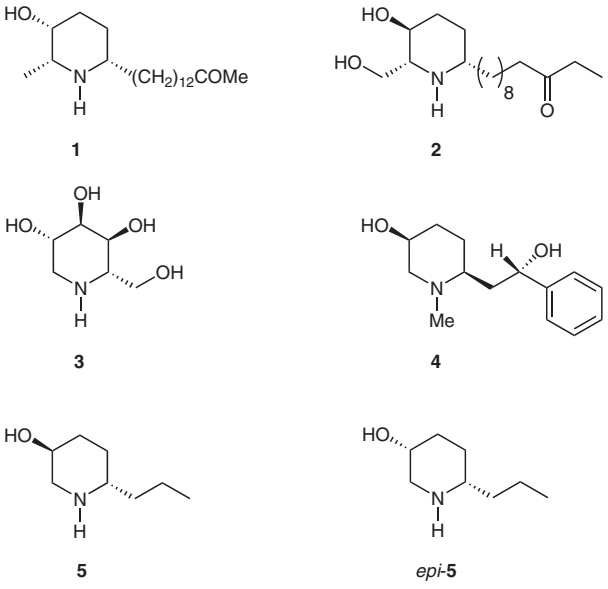
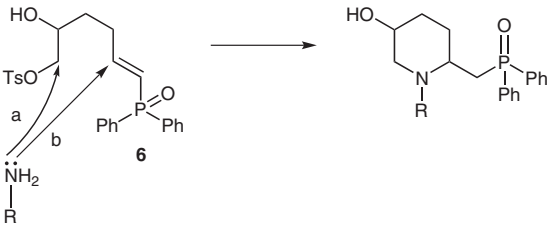


Figure 1 Important types of naturally occurring 3(5)-hydroxypiperidines



Scheme 1 Domino process of nucleophilic attack (a) and Michael-type addition (b) of a primary amine on 2-hydroxy-6-diphenylphosphinyl-5-hexenyl tosylate (**6**)

The key intermediate is 2-hydroxy-6-diphenylphosphinyl-5-hexenyl tosylate (**6**). We had reported earlier that this compound could be prepared conveniently by addition of tosylated glycidol to the anion of phosphine oxide **7** (Scheme 2).[13] If toluene is employed as the solvent, the reaction proceeds with high γ-selectivity, that is, at the unsubstituted terminus of the allyl system to create the electron-poor alkene double bond in **6**.[13] Thus, together with

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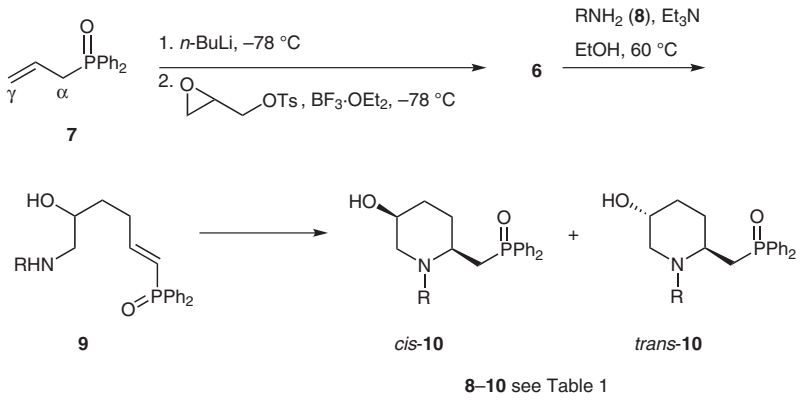


Scheme 2 Formation of phosphine intermediate **6** and subsequent domino reactions with primary amines **8**

the tosyloxy-substituted carbon, intermediate **6** represents a dication equivalent. The reaction with primary amines, which can act as bidentate nucleophiles, should allow the domino process outlined in Scheme 1.

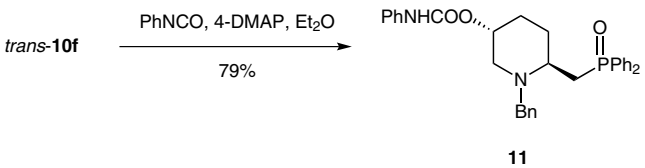
The reaction of **6** with model amine **8h** turned out to be rather slow. The optimum conditions involved heating the reaction mixture at 60 °C in methanol or ethanol in the presence of triethylamine for two days to give a 65–68% yield of the cyclization product **10h** (Scheme 2). In *tert*-butyl alcohol as the solvent and using potassium *tert*-butoxide, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or triethylamine as the catalyst, the yields of piperidinol **10h** were only 25%, 29% and 40%, respectively. The use of pyridine in ethanol as the solvent resulted in a 51% yield of **10h**. The reaction proceeded successfully with unbranched primary amines **8a**–**c**, as well as with amines **8f**,**g** containing unsaturation and functionalized amines **8h**,**i** (Table 1). However, under the standard reaction conditions, the sterically hindered amine **8d** and less nucleophilic aniline (**8e**) reacted via the S_N2 process to yield substitution products **9d**,**e** (Table 1); more vigorous conditions resulted in decomposition. It was not possible to employ N-unsubstituted amides such as benzamide in the tandem cyclization as only complex mixtures were obtained. The formation of amines **9d**,**e** indicates that the successful domino cyclizations of the other amines **8** are initiated by the substitution step, and that this is followed by a Michael-type addition to the vinyl phosphine unit in intermediates **9a**–**c**,**f**–**i**, and not via the reverse sequence. This reaction course is in line with the mechanism proposed by Bunce et al. for the cyclization of ω-iodo-alkenoates with benzylamine.[14] The same should hold for a mesylate substitution and Michael sequence of mesyloxy-alkenoates.[15]

The Michael-type addition of the secondary amine unit in **9** may occur at the *Re* or *Si* face of the vinyl phosphine moiety. In fact, piperidinols **10** were formed as mixtures of diastereomers. The diastereoselectivity was moderate (Table 1), but the two diastereomers could be separated easily by column chromatography, with the minor diastereomer being eluted first. We found it difficult to assign

Table 1 Cyclization of Alkene **6** with Different Primary Amines **8**

Amine	Product (total yield)	Yield of *cis*-**10**	Yield of *trans*-**10**
$EtNH_2$ (**8a**)	**10a** (62%)	30%	29%
n-$PrNH_2$ (**8b**)	**10b** (87%)	31%	36%
$BuNH_2$ (**8c**)	**10c** (86%)	42%	28%
t-$BuNH_2$ (**8d**)	**9d** (73%)	–	–
$PhNH_2$ (**8e**)	**9e** (54%)	–	–
$BnNH_2$ (**8f**)	**10f** (85%)	36%	48%
$allylNH_2$ (**8g**)	**10g** (73%)	37%	35%
$H_2NCH_2CH(OMe)_2$ (**8h**)	**10h** (68%)	34%	34%
$H_2NCH_2CH_2OTBDMS$ (**8i**)	**10i** (78%)	22%	56%

the *cis*- or *trans*-configuration to these diastereomers based on the NMR coupling constants. After some experimentation, we observed that a crystalline phenyl urethane **11** was formed from the predominating diastereomer of piperidinol **10f** and phenyl isocyanate (Scheme 3). An X-ray structural investigation of a suitable crystal revealed the *trans*-arrangement of the 5-carbamate and the 2-phosphinylmethyl substituents (Figure 2).[16] Hence the starting material was *trans*-**10f**, which is consequently the major diastereomer and that which eluted second. Based on this information, comparison of the NMR data of **10f** with the other piperidinols **10** allowed assignment of the configurations of all products **10** (Table 1).



Scheme 3 Addition of phenyl isocyanate to piperidinol *trans*-**10f** to give carbamate **11**

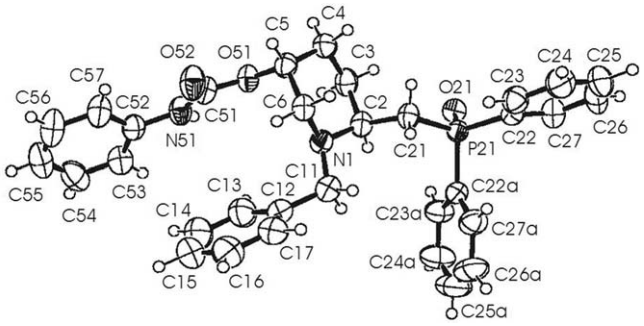
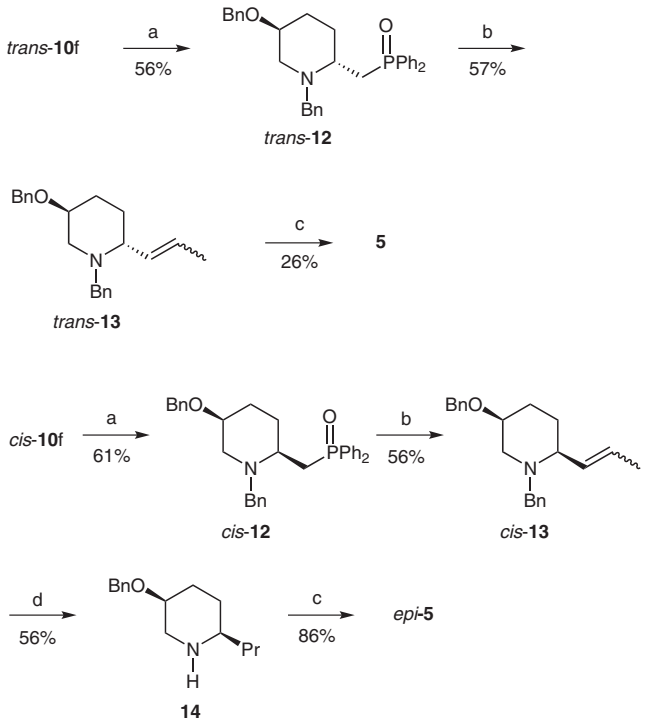


Figure 2 X-ray crystal structure of *trans*-*N*-phenyl urethane derivative **11**

In addition to the convenient one-step formation of piperidinols from a readily accessible precursor and different amines as the nitrogen source, the presence of the phosphine oxide unit in **10** is an especially attractive feature for subsequent Horner olefination chemistry. In this context, an obvious target among naturally occurring piperidinols was pseudoconhydrine (**5**; Figure 1). This synthesis would require removal of the exocyclic substituent on nitrogen in precursor **10**, which should be possible, most conveniently, with the benzyl residue in **10f**. As this compound is available in both its *cis* and *trans* forms, a synthesis of the unnatural diastereomer, *epi*-pseudoconhydrine (*epi*-**5**), can be envisaged using the same synthetic manipulations starting from *cis*-**10f** (Scheme 4).



Scheme 4 Synthesis of pseudoconhydrine (**5**) and the unnatural diastereomer, *epi*-**5**. *Reagents and conditions*: (a) (1) NaH, THF, 0 °C to r.t.; (2) BnBr, Bu_4NI (0.2 equiv), 50 °C, 12 h; (b) (1) *n*-BuLi, THF, –78 °C; (2) MeCHO, –78 °C → 0 °C; (3) NaH, DMF, 60 °C; (c) H_2, Pd/C, HCl, MeOH; (d) H_2, $Pd(OH)_2$/C, HCl, EtOH.

To allow the use of a strong base in the olefination chemistry, the secondary alcohol functionality of diastereomer *trans*-**10f** [isolated by column chromatography from the reaction of **6** and benzylamine (see Scheme 3)] was protected by benzylation to give *trans*-**12** (Scheme 4). Chain elongation of the C-2 substituent was achieved by a two-step Horner reaction using acetaldehyde as the carbonyl component. The reaction first provided the α-hydroxy addition product, which was transformed into the alkene, *trans*-**13**, using sodium hydride and *N*,*N*-dimethylformamide at 60 °C. The product was formed with moderate *trans*-selectivity (*E*/*Z* = 67:33), which may reflect the similar steric requirements of the diphenylphosphinyl group and the piperidine heterocycle in the Horner intermediate. Reductive removal of the *O*- and *N*-benzyl protecting groups and simultaneous reduction of the double bond was achieved by hydrogenation using palladium on carbon as the catalyst to provide the target molecule, pseudoconhydrine (**5**). The structure of **5** was confirmed by comparison of its NMR data,[11h,12h] and those of its hydrochloride salt (**5**·HCl)[12r] with literature values, which proved to be identical.

The synthesis of *epi*-**5** was achieved along similar lines (Scheme 4). In a modification, the reduction of alkene **13** into *epi*-**5** was carried out in two steps, as the direct conversion of *trans*-**13** into **5** gave a rather modest yield. Initial exposure of *cis*-**13** to an atmosphere of hydrogen in the presence of Pearlman's catalyst [$Pd(OH)_2$/C] in ethanol–hydrochloric acid gave the partly cleaved and reduced product **14**. As expected, in the presence of the amine function,[17] the O–Bn bond survived the reduction reaction. In a second hydrogenation step using palladium on charcoal (Pd/C) as the catalyst, *epi*-pseudoconhydrine (*epi*-**5**) was formed. The structural assignment of *epi*-**5** was based on the spectroscopic data, which were quite similar to those of pseudoconhydrine (**5**).

In summary, we have presented a straightforward, amine-induced domino cyclization of the phosphinyl-substituted alcohol **6** to give 2-substituted piperidin-5-ols. Both diastereomers could be isolated by chromatography. The method was also applied to the synthesis of pseudoconhydrine (**5**) and *epi*-pseudoconhydrine (*epi*-**5**) in only three or four additional steps following the cyclization. It should be noted that the procedure may easily be utilized for the synthesis of optically active **5** and *epi*-**5** if the allyl derivative **7** is reacted with an enantiomerically enriched glycidol tosylate. This chiral substrate is readily available by Sharpless epoxidation of allyl alcohol[18] and subsequent tosylation.[19]

Reactions requiring anhydrous conditions were performed under nitrogen. The amines used in this research were purchased from commercial sources, except for amine **8h**.[20] Column or flash column chromatography was performed on Macherey–Nagel silica gel (60, 230–400 mesh). Petroleum ether (PE) refers to the fraction boiling in the 60–70 °C range. Melting points were recorded using a Büchi instrument according to Dr. Tottoli apparatus and are uncorrected. FTIR spectra were measured on a Bruker Vektor 22 FT spectrophotometer. NMR spectra were measured at 400 MHz or 200 MHz

(^{1}H), 100 or 50 MHz (^{13}C) and 162 MHz (^{31}P) on Bruker ARX-400 and DPX-200 instruments. Deuterated chloroform was used as the solvent unless otherwise stated. Chemical shifts (δ) are reported relative to tetramethylsilane (δ = 0 ppm) as an internal standard for ^{1}H and ^{13}C spectra in $CDCl_3$, $Me_3SiCD_2CD_2COONa$ (δ_{Me} = 0 ppm) for spectra in D_2O, and external trimethyl phosphite (shifts corrected for 80% aq H_3PO_4 with δ = 0 ppm) for ^{31}P NMR spectra. MS spectra were recorded using a Hewlett Packard HP 5989 B spectrometer. High-resolution mass spectra (HRMS) were obtained using a VG Autospec instrument at the Institut für Organische Chemie, Leibniz-Universität Hannover. Elemental analyses were performed using a Carlo Erba 1106 analyzer at the Institut für Pharmazeutische Chemie, TU Braunschweig.

cis- and *trans*-1-Ethyl-6-(diphenylphosphinylmethyl)piperidin-3-ol (10a); General Procedure

A solution of alkene **6**[13] (361 mg, 0.768 mmol), ethylamine (0.38 mL, 2 M in MeOH, 0.768 mmol) and anhydrous Et_3N (0.118 mL, 0.845 mmol) in anhydrous EtOH (4.2 mL) was heated at 60 °C for 2.5 d. The mixture was allowed to cool and then concentrated in vacuo. The residue was dissolved in a mixture of Et_2O–CH_2Cl_2 (10 mL, 2:1). The organic layer was washed with 1 M NaOH (3 × 5 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude mixture of isomeric products was purified by flash column chromatography (EtOAc–EtOH–Et_3N, 40:1:0.5) to give *cis*-**10a** (79 mg, 30%), a mixture of *cis*- and *trans*-**10a** (8 mg, 3%) and *trans*-**10a** (77 mg, 29%); total yield: 164 mg (62%).

cis-10a

Yellow solid; mp 43 °C.

IR (KBr): 3412, 3055, 2929, 1655, 1591, 1438, 1162, 1119, 696 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.92 (t, ^3J = 7.2 Hz, 3 H), 1.38–1.82 (m, 4 H), 2.39–2.73 (m, 6 H), 2.97–3.36 (m, 2 H, CH, OH), 3.70–3.87 (m, 1 H), 7.39–7.58 (m, 6 H), 7.67–7.85 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.3, 26.5, 29.0, 29.3 (d, J_{PC} = 69.2 Hz), 47.5, 54.2, 54.9, 64.6, 128.8, 128.9, 130.6, 130.6 (d, J_{PC} = 9.2 Hz, 2 C), 132.0 (d, J_{PC} = 3.1 Hz, 2 C), 132.6 (d, J_{PC} = 100.7 Hz), 132.9 (d, J_{PC} = 99.7 Hz).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 30.0.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{20}H_{26}NO_2P$: 343.1701; found: 343.1701.

trans-10a

Yellow solid; mp 45 °C.

IR (KBr): 3383, 3058, 2964, 2932, 2857, 1652, 1591, 1439, 1178, 1119, 697 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.90 (t, ^3J = 7.2 Hz, 3 H), 1.34–1.83 (m, 4 H), 2.30–2.58 (m, 5 H), 2.74 (dd, ^2J = 11.9 Hz, ^3J = 2.4 Hz, 1 H), 3.04–3.22 (m, 1 H), 3.69 (br s, 1 H, OH), 3.72–3.84 (m, 1 H), 7.39–7.58 (m, 6 H), 7.69–7.83 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.3, 26.1 (d, J_{PC} = 69.2 Hz), 26.5, 28.5, 47.6, 52.9, 54.2, 64.9, 128.7, 128.8, 130.5, 130.7 (each d, J_{PC} = 9.2 Hz, 2 C), 131.9 (d, J_{PC} = 2.0 Hz, 2 C), 132.6, 133.4 (each d, J_{PC} = 99.7 Hz).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 30.3.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{20}H_{26}NO_2P$: 343.1701; found: 343.1701.

cis- and *trans*-1-Propyl-6-(diphenylphosphinylmethyl)piperidin-3-ol (10b)

Reaction of alkene **6** (470 mg, 1 mmol) and *n*-propylamine (0.083 mL, 1 mmol) using the general procedure, and purification by flash column chromatography (EtOAc–EtOH–Et_3N, 40:1:0.5) gave *cis*-**10b** (109 mg, 31%), a mixture of *cis*- and *trans*-**10b** (70 mg, 20%) and *trans*-**10b** (129 mg, 36%); total yield: 308 mg (87%).

cis-10b

Pale yellow solid; mp 38 °C.

IR (KBr): 3347, 3056, 2932, 1662, 1591, 1438, 1169, 1119, 719, 698 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.75 (t, ^3J = 7.4 Hz, 3 H), 1.17–1.82 (m, 6 H), 2.19–2.67 (m, 6 H), 2.59 (dd, ^2J = 11.3 Hz, ^3J = 3.8 Hz, 1 H), 3.09 (dddt, ^3J = 8.7 Hz, ^3J = 8.5 Hz, ^3J = 4.0 Hz, $^3J_{PH} \approx$ 2.0 Hz, 1 H), 3.72 (dddd, ^3J = 8.0 Hz, ^3J = 8.0 Hz, ^3J = 4.0 Hz, ^3J = 4.0 Hz, 1 H), 7.39–7.57 (m, 6 H), 7.68–7.83 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.7, 19.8, 26.6 (d, J_{PC} = 69.5 Hz), 27.8, 29.1, 52.4, 55.1, 55.8, 66.3, 128.5, 128.8, 130.5, 130.7 (each d, J_{PC} = 9.2 Hz, 2 C), 131.69, 131.70 (each d, J_{PC} = 2.4 Hz), 133.1 (d, J_{PC} = 98.7 Hz), 133.8 (d, J_{PC} = 99.1 Hz).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 30.3.

trans-10b

Pale yellow solid; mp 36 °C.

IR (KBr): 3375, 3057, 2963, 2930, 2872, 1656, 1591, 1438, 1160, 1120, 699 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.77 (t, ^3J = 7.3 Hz, 3 H), 1.07–1.78 (m, 6 H), 2.14–2.54 (m, 5 H), 2.75 (dd, ^2J = 11.9 Hz, ^3J = 2.1 Hz, 1 H), 3.10–3.26 (m, 1 H), 3.73–3.84 (m, 1 H), 4.70 (br s, 1 H, OH), 7.39–7.58 (m, 6 H), 7.61–7.85 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.6, 19.6, 25.2 (d, J_{PC} = 69.2 Hz), 25.9, 27.8, 53.0, 54.2, 55.7, 64.9, 128.6, 128.8, 130.5 (d, J_{PC} = 10.2 Hz, 2 C), 130.7 (d, J_{PC} = 9.2 Hz, 2 C), 131.8 (d, J_{PC} = 3.1 Hz, 2 C), 132.6 (d, J_{PC} = 98.7 Hz), 133.5 (d, J_{PC} = 99.7 Hz).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 30.5.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{21}H_{28}NO_2P$: 357.1858; found: 357.1858.

cis- and *trans*-1-Butyl-6-(diphenylphosphinylmethyl)piperidin-3-ol (10c)

Reaction of alkene **6** (354 mg, 0.75 mmol) and *n*-butylamine (0.07 mL, 0.75 mmol) using the general procedure, and purification by flash column chromatography (EtOAc–EtOH–Et_3N, 40:1:0.5) gave *cis*-**10c** (117 mg, 42%), a mixture of *cis*- and *trans*-**10c** (43 mg, 15.5%) and *trans*-**10c** (79 mg, 28.4%); total yield: 239 mg (85.9%).

cis-10c

Pale yellow solid; mp 42 °C.

IR (KBr): 3385, 3057, 2930, 2869, 1657, 1591, 1438, 1163, 1119, 695 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.80 (t, ^3J = 7.3 Hz, 3 H), 1.06–1.82 (m, 8 H), 2.16–2.52 (m, 6 H), 2.59 (dd, ^2J = 11.3 Hz, ^3J = 3.5 Hz, 1 H), 3.08 (dddt, ^3J = 8.7 Hz, ^3J = 8.5 Hz, ^3J = 4.3 Hz, $^3J_{PH} \approx$ 2.5 Hz, 1 H), 3.72 (dddd, ^3J = 8.0 Hz, ^3J = 8.0 Hz, ^3J = 4.0 Hz, ^3J = 4.0 Hz, 1 H), 7.38–7.58 (m, 6 H), 7.67–7.84 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9, 20.4, 27.2 (d, J_{PC} = 70.0 Hz), 28.3 (d, J_{PC} = 1.5 Hz), 28.8, 29.3, 52.5, 53.6, 55.3, 66.4, 128.5, 128.8 (each d, J_{PC} = 1.5 Hz, 2 C), 130.5, 130.7 (each d, J_{PC} = 9.2 Hz, 2 C), 131.70, 131.71 (each d, J_{PC} = 2.4 Hz, 2 C), 133.2, 133.9 (d, J_{PC} = 98.7 Hz).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 30.2.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{22}H_{30}NO_2P$: 371.2014; found: 371.2014.

trans-10c

Pale yellow solid; mp 33 °C.

IR (KBr): 3355, 3057, 2933, 2870, 1660, 1591, 1438, 1181, 1120, 698 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.80 (t, ^3J = 7.2 Hz, 3 H), 1.07–1.73 (m, 8 H), 2.18–2.51 (m, 5 H), 2.67 (dd, ^2J = 11.8 Hz, ^3J = 2.0

Hz, 1 H), 3.04 (br s, 1 H, OH), 3.10–3.30 (m, 1 H), 3.70–3.81 (m, 1 H), 7.39–7.59 (m, 6 H), 7.68–7.84 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.8, 20.3, 24.4 (d, J_{PC} = 69.5 Hz), 25.7, 27.5, 28.9, 52.6, 53.7, 54.0, 65.1, 128.6, 128.8 (each 2 C), 130.5, 130.8 (each d, J_{PC} = 9.2 Hz, 2 C), 131.8 (d, J_{PC} = 2.4 Hz, 2 C), 132.8, 133.8 (each d, J_{PC} = 99.1 Hz).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 30.5.

Anal. Calcd for $C_{22}H_{30}NO_2P$: C, 71.14; H, 8.14; N, 3.77. Found: C, 71.45; H, 8.35; N, 3.63.

(*E*)-[5-Hydroxy-6-(*tert*-butylamino)-1-hexenyl]diphenylphosphine Oxide (9d)

Reaction of alkene **6** (470 mg, 1.0 mmol) and *tert*-butylamine (0.11 mL, 1.0 mmol) using the general procedure gave the crude product **9d** (272 mg, 73%) as an orange viscous oil, which was characterized without further purification.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.11 (s, 9 H), 1.52–1.66 (m, 2 H), 2.36 (dd, ^2J = 11.8 Hz, ^3J = 9.0 Hz, 1 H), 2.42–2.64 (m, 2 H), 2.73 (dd, ^2J = 11.8 Hz, ^3J = 3.0 Hz, 1 H), 2.83 (br s, 2 H), 3.46–3.61 (m, 1 H), 6.27 (ddt, ^3J = 17.0 Hz, ^4J = 1.5 Hz, $^2J_{PH}$ = 24.4 Hz, 1 H), 6.74 (ddt, ^3J = 17.0 Hz, ^3J = 6.4 Hz, $^3J_{PH}$ = 19.5 Hz, 1 H), 7.37–7.57 (m, 6 H), 7.60–7.75 (m, 4 H).

(*E*)-[5-Hydroxy-6-(phenylamino)-1-hexenyl]diphenylphosphine Oxide (9e)

Reaction of alkene **6** (595 mg, 1.27 mmol) and aniline (0.12 mL, 1.27 mmol) using the general procedure, and purification by flash column chromatography (EtOAc–EtOH–Et_3N, 50:1:0.5) gave **9e** (269 mg, 54%).

Pale orange solid; mp 38 °C.

IR (KBr): 3352, 3054, 3023, 2927, 1635, 1603, 1437, 1173, 1121, 1102, 997, 809, 753, 722, 694 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.60–1.78 (m, 2 H), 2.28–2.63 (m, 2 H), 3.00 (dd, ^2J = 12.7 Hz, ^3J = 8.2 Hz, 1 H), 3.20 (dd, ^2J = 12.7 Hz, ^3J = 3.4 Hz, 1 H), 3.74–3.92 (m, 1 H), 6.26 (ddt, ^3J = 17.1 Hz, ^4J = 1.5 Hz, $^2J_{PH}$ = 24.4 Hz, 1 H), 6.25–6.76 (m, 3 H), 6.74 (ddt, ^3J = 17.1 Hz, ^3J = 6.4 Hz, $^3J_{PH}$ = 19.8 Hz, 1 H), 7.07–7.20 (m, 2 H), 7.35–7.57 (m, 6 H), 7.58–7.75 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.7 (d, J_{PC} = 17.0 Hz, 1 C), 33.1, 50.2, 69.2, 113.1 (2 C), 117.6, 121.9 (d, J_{PC} = 103.0 Hz, 1 C), 128.6 (d, J_{PC} = 12.2 Hz, 4 C), 129.2 (2 C), 131.2 (d, J_{PC} = 10.2 Hz, 4 C), 131.8 (d, J_{PC} = 2.9 Hz, 2 C), 132.8 (d, J_{PC} = 105.5 Hz, 2 C), 148.3, 152.2 (d, J_{PC} = 2.4 Hz, 1 C).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 23.5.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{24}H_{26}NO_2P$: 391.1701; found: 391.1701.

***cis*- and *trans*-1-Benzyl-6-(diphenylphosphinylmethyl)piperidin-3-ol (10f)**

Reaction of alkene **6** (5.283 g, 11.238 mmol) and benzylamine (1.226 mL, 11.238 mmol) using the general procedure, and purification by flash column chromatography (EtOAc–EtOH–Et_3N, 30:1:0.5) gave *cis*-**10f** (1.279 g, 28.1%), a mixture of *cis*- and *trans*-**10f** (ratio 1:5, 2.234 g, 49.1%) and *trans*-**10f** (0.33 g, 7.3%); total yield: 3.846 g (85%).

***cis*-10f**

Pale yellow solid; mp 58 °C.

IR (KBr): 3333, 3059, 3027, 2936, 2867, 2802, 1665, 1591, 1438, 1177, 1120, 695 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.40–1.88 (m, 4 H), 2.04 (br s, 1 H, OH), 2.40 (dd, ^2J = 11.6 Hz, ^3J = 8.0 Hz, 1 H), 2.46–2.61 (m, 3 H), 3.17 (dddt, ^3J = 8.8 Hz, ^3J = 8.8 Hz, ^3J = 4.4 Hz, J_{PH} = 2.5 Hz, 1 H), 3.36, 3.64 (each d, ^2J = 13.6 Hz, 1 H), 3.69 (dddd, ^3J = 8.0 Hz, ^3J = 8.0 Hz, ^3J = 4.0 Hz, ^3J = 4.0 Hz, 1 H), 7.15–7.29 (m, 5 H), 7.37–7.57 (m, 6 H), 7.62–7.81 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.1 (d, J_{PC} = 69.3 Hz), 28.1, 29.1, 53.4, 54.5, 58.4, 66.5, 127.0, 128.4, 128.2 (each 2 C), 128.7 (d, J_{PC} = 11.5 Hz, 4 C), 130.5 (d, J_{PC} = 9.2 Hz), 130.7 (d, J_{PC} = 9.0 Hz), 131.7 (d, J_{PC} = 3.0 Hz), 132.9 (d, J_{PC} = 98.4 Hz), 133.9 (d, J_{PC} = 98.4 Hz), 138.8.

^{31}P NMR (162 MHz, $CDCl_3$): δ = 30.3.

Anal. Calcd for $C_{25}H_{28}NO_2P$: C, 74.05; H, 6.96; N, 3.45. Found: C, 73.61; H, 6.94; N, 3.17.

***trans*-10f**

Pale yellow solid; mp 56 °C.

IR (KBr): 3354, 3056, 3026, 2932, 2859, 2798, 1661, 1591, 1437, 1181, 1119, 742, 696 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.48–1.86 (m, 3 H), 1.95–2.17 (m, 1 H), 2.37 (dd, ^2J = 12.0 Hz, ^3J = 4.4 Hz, 1 H), 2.51 (dd, ^2J = 12.6 Hz, ^3J = 6.6 Hz, 2 H), 2.69 (dd, ^2J = 12.0 Hz, ^3J = 2.0 Hz, 1 H), 3.15–3.32 (m, 1 H), 3.38 (d, ^2J = 13.6 Hz, 1 H), 3.54 (d, ^2J = 13.2 Hz, 1 H), 3.72 (m_c, 1 H), 7.14–7.34 (m, 5 H), 7.38–7.58 (m, 6 H), 7.67–7.79 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.1 (d, J_{PC} = 68.8 Hz), 25.8, 27.4, 53.4, 54.5, 58.6, 65.2, 127.2, 128.4, 128.6 (2 C), 128.70, 128.73 (d, J_{PC} = 11.6 Hz, 2 C), 130.5, 130.8 (d, J_{PC} = 9.2 Hz, 2 C), 131.7 (d, J_{PC} = 2.0 Hz), 131.8 (d, J_{PC} = 3.0 Hz), 132.6 (d, J_{PC} = 99.6 Hz), 133.9 (d, J_{PC} = 99.6 Hz), 138.3.

^{31}P NMR (162 MHz, $CDCl_3$): δ = 30.3.

Anal. Calcd for $C_{25}H_{28}NO_2P$: C, 74.05; H, 6.96; N, 3.45. Found: C, 73.45; H, 7.07; N, 3.43.

***cis*- and *trans*-1-Allyl-6-(diphenylphosphinylmethyl)piperidin-3-ol (10g)**

Reaction of alkene **6** (715 mg, 1.52 mmol) and allylamine (0.114 mL, 1.52 mmol) using the general procedure, and purification by flash column chromatography (EtOAc–EtOH–Et_3N, 40:1:0.5) gave *cis*-**10g** (199 mg, 37%), a mixture of *cis*- and *trans*-**10g** (4 mg, 1%), and *trans*-**10g** (188 mg, 35%); total yield: 391 mg (73%).

***cis*-10g**

Pale yellow solid; mp 41 °C.

IR (KBr): 3348, 3077, 3058, 2935, 2869, 2805, 1643, 1591, 1438, 1178, 1120, 751, 699 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.40–1.83 (m, 4 H), 2.37–2.67 (m, 4 H), 2.94, 3.10 (each ddt, ^2J = 14.0 Hz, ^3J = 6.4 Hz, ^4J = 1.4 Hz, 1 H), 2.95–3.13 (m, 1 H), 3.73 (dddd, ^3J = 7.6 Hz, ^3J = 7.6 Hz, ^3J = 3.8 Hz, ^3J = 3.8 Hz, 1 H), 4.99–5.13 (m, 2 H), 5.66 (ddt, ^3J = 17.0 Hz, ^3J = 10.2 Hz, ^3J = 6.4 Hz, 1 H), 7.39–7.57 (m, 6 H), 7.67–7.83 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.8 (d, J_{PC} = 69.4 Hz), 27.8 (d, J_{PC} = 2.0 Hz), 29.4, 53.3, 55.1, 57.2, 66.2, 117.5, 128.5, 128.8 (each 2 C), 130.5 (d, J_{PC} = 9.7 Hz, 2 C), 130.7 (d, J_{PC} = 9.2 Hz, 2 C), 131.7 (d, J_{PC} = 2.4 Hz, 2 C), 133.2 (d, J_{PC} = 98.2 Hz), 133.9 (d, J_{PC} = 99.1 Hz), 135.1.

^{31}P NMR (162 MHz, $CDCl_3$): δ = 30.1.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{21}H_{26}NO_2P$: 355.1701; found: 355.1701.

***trans*-10g**

Pale yellow solid; mp 48 °C.

IR (KBr): 3339, 3077, 3058, 2935, 2862, 2806, 1641, 1591, 1438, 1183, 1120, 751, 698 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.37–1.77 (m, 3 H), 1.95–2.10 (m, 1 H), 2.33–2.49 (m, 2 H), 2.42 (dd, ^2J = 12.6 Hz, ^3J = 8.8 Hz, 1 H), 2.70 (dd, ^2J = 12.0 Hz, ^3J = 2.4 Hz, 1 H), 2.89, 3.04 (each ddt, ^2J = 14.0 Hz, ^3J = 6.4 Hz, ^4J = 1.4 Hz, 1 H), 3.08–3.30 (m, 1 H), 3.73 (dddd, ^3J = 5.2 Hz, ^3J = 5.2 Hz, ^3J = 2.6 Hz, ^3J = 2.6 Hz, 1 H),

4.98–5.11 (m, 2 H), 5.67 (ddt, ^3J = 17.6 Hz, ^3J = 9.6 Hz, ^3J = 6.4 Hz, 1 H), 7.39–7.57 (m, 6 H), 7.68–7.82 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.7 (d, J_{PC} = 69.7 Hz), 26.4, 28.2, 53.3, 54.2, 57.3, 65.4, 117.7, 128.6, 128.8 (each 2 C), 130.5 (d, J_{PC} = 9.2 Hz, 2 C), 130.8 (d, J_{PC} = 9.2 Hz, 2 C), 131.8 (d, J_{PC} = 2.4 Hz, 2 C), 132.8 (d, J_{PC} = 98.2 Hz), 133.8 (d, J_{PC} = 99.6 Hz), 135.1.

^{31}P NMR (162 MHz, $CDCl_3$): δ = 30.4.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{21}H_{26}NO_2P$: 355.1701; found: 355.1701.

***cis*- and *trans*-1-(2,2-Dimethoxyethyl)-6-(diphenylphosphinylmethyl)piperidin-3-ol (10h)**

Reaction of alkene **6** (1.88 g, 4 mmol) and 2,2-dimethoxyethanamine (0.436 mL, 4 mmol) using the general procedure, and purification by flash column chromatography (EtOAc–EtOH–Et_3N, 30:1:0.5) gave the diastereomers of **10h** in equal amounts; total yield: 1.097 g (68%).

***cis*-10h**

Orange oil.

IR (film): 3347, 3056, 2937, 1438, 1175, 750, 720, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (m_c, 1 H), 1.66 (m_c, 1 H), 1.76 (m_c, 2 H), 2.44–2.62 (m, 6 H), 2.73 (dd, ^2J = 11.6 Hz, ^3J = 4.0 Hz, 1 H), 3.13 (m_c, 1 H), 3.25, 3.29 (each s, 3 H), 3.71 (ddd, ^3J = 12.4 Hz, ^3J = 8.0 Hz, ^3J = 4.0 Hz, 1 H), 4.27 (t, ^3J = 5.2 Hz, 1 H), 7.47 (m_c, 6 H), 7.75 (m_c, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 27.0 (d, J_{PC} = 69.5 Hz), 27.4 (d, J_{PC} = 2.0 Hz), 28.8, 53.1, 53.7, 53.8, 55.7, 55.9, 66.1, 128.6 (d, J_{PC} = 11.7 Hz, 4 C), 103.3, 130.4, 130.7 (each d, J_{PC} = 9.2 Hz, 2 C), 131.7 (d, J_{PC} = 2.4 Hz, 2 C), 132.8 (d, J_{PC} = 99.1 Hz), 133.7 (d, J_{PC} = 98.7 Hz).

Anal. Calcd for $C_{22}H_{30}NO_4P$: C, 65.49; H, 7.49; N, 3.47. Found: C, 65.11; H, 7.35; N, 3.38.

***trans*-10h**

Orange oil.

IR (film): 3355, 3056, 2934, 2831, 1591, 1438, 1184, 750, 664 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46–1.68 (m, 3 H), 2.04 (m_c, 1 H), 2.36–2.51 (m, 4 H), 2.53 (dd, ^2J = 12.3 Hz, ^3J = 4.0 Hz, 1 H), 2.82 (br s, 1 H, OH), 2.81 (dd, ^2J = 12.3 Hz, ^3J = 2.0 Hz, 1 H), 3.19 (m_c, 1 H), 3.24, 3.30 (each s, 3 H), 3.74 (m_c, 1 H), 4.26 (t, ^3J = 5.4 Hz, 1 H), 7.44–7.56 (m, 6 H), 7.76 (m_c, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 25.5 (d, J_{PC} = 70.5 Hz), 25.6, 27.2, 53.7, 53.8, 54.7, 55.6, 55.7, 65.1, 103.2, 128.69, 128.72 (each d, J_{PC} = 11.6 Hz, 2 C), 130.5, 130.8 (each d, J_{PC} = 9.5 Hz, 2 C), 131.8 (d, J_{PC} = 2.8 Hz, 2 C), 132.8 (d, J_{PC} = 98.5 Hz), 133.8 (d, J_{PC} = 100.1 Hz).

Anal. Calcd for $C_{22}H_{30}NO_4P$: C, 65.49; H, 7.49; N, 3.47. Found: C, 65.30; H, 7.79; N, 3.60.

***cis*- and *trans*-1-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-6-(diphenylphosphinylmethyl)piperidin-3-ol (10i)**

Reaction of alkene **6** (230 mg, 0.49 mmol) and 2-(*tert*-butyldimethylsiloxy)ethylamine (86 mg, 0.49 mmol) using the general procedure, and purification by flash column chromatography (EtOAc–EtOH–Et_3N, 30:1:0.5) gave *cis*-**10i** (50 mg, 22%), and *trans*-**10i** (131 mg, 56%); total yield: 181 mg (78%).

***cis*-10i**

Orange viscous oil.

IR (film): 3347, 3057, 2930, 2856, 1591, 1438, 1254, 1180, 1118, 836 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.01 (s, 6 H), 0.84 (s, 9 H), 1.45, 1.62 (each m_c, 1 H), 1.71 (m_c, 2 H), 2.35–2.60 (m, 6 H), 2.65 (dd, ^2J = 12.0 Hz, ^3J = 3.6 Hz, 1 H), 3.04 (dddt, ^3J = 8.4 Hz, ^3J = 8.0 Hz, ^3J = 4.0 Hz, J_{PC} = 2.5 Hz, 1 H), 3.50 (t, ^3J = 6.6 Hz, 2 H), 3.69 (dddd, ^3J = 8.0 Hz, ^3J = 8.0 Hz, ^3J = 4.0 Hz, ^3J = 4.0 Hz, 1 H), 7.46 (m_c, 6 H), 7.74 (m_c, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = –5.38, –5.36, 18.2, 25.9, 27.8 (d, J_{PC} = 2.0 Hz), 27.9 (d, J_{PC} = 69.9 Hz), 29.1, 53.5, 56.1 (2 C), 61.4, 66.1, 128.6 (d, J_{PC} = 11.9 Hz, 4 C), 130.5, 130.7 (each d, J_{PC} = 9.3 Hz, 2 C), 131.7 (d, J_{PC} = 2.8 Hz, 2 C), 133.0 (d, J_{PC} = 98.9 Hz), 133.8 (d, J_{PC} = 99.3 Hz).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 30.7.

Anal. Calcd for $C_{26}H_{40}NO_3PSi$: C, 65.93; H, 8.51; N, 2.96. Found: C, 65.13; H, 8.63; N, 2.84.

***trans*-10i**

Orange viscous oil.

IR (film): 3356, 3057, 2929, 2856, 1591, 1438, 1254, 1183, 836 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.00 (s, 6 H), 0.85 (s, 9 H), 1.46–1.68 (m, 3 H), 2.02 (m, 1 H), 2.34–2.55 (m, 6 H), 2.77 (dd, ^2J = 11.9 Hz, ^3J = 2.1 Hz, 1 H), 3.16 (m_c, 1 H), 3.51 (t, ^3J = 6.2 Hz, 2 H), 3.73 (m_c, 1 H), 7.48 (m, 6 H), 7.76 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = –5.4, 18.2, 25.5 (d, J_{PC} = 69.0 Hz), 25.6, 25.9, 27.4, 53.5, 54.4, 56.2, 61.2, 65.1, 128.68, 128.70 (each d, J_{PC} = 11.9 Hz, 2 C), 130.5, 130.8 (each d, J_{PC} = 9.2 Hz, 2 C), 131.76, 131.78 (each d, J_{PC} = 2.8 Hz, 2 C), 132.8 (d, J_{PC} = 99.1 Hz), 133.8 (d, J_{PC} = 99.9 Hz).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 31.0.

Anal. Calcd for $C_{26}H_{40}NO_3PSi$: C, 65.93; H, 8.51; N, 2.96. Found: C, 65.47; H, 8.56; N, 2.74.

***trans*-1-Benzyl-6-(diphenylphosphinylmethyl)piperidin-3-yl *N*-Phenylcarbamate (11)**

To a vigorously stirred suspension of *trans*-**10f** (202.5 mg, 0.5 mmol) in Et_2O (1 mL) was added phenyl isocyanate (0.054 mL, 0.5 mmol) and Et_3N (1 drop). After 24 h without significant reaction, DMAP (6.1 mg, 0.05 mmol) was added. Stirring was continued for another 12 h. The mixture was triturated with PE (4 mL), and the remaining solid removed by filtration and then washed with PE (3 × 1 mL). Crystallization from benzene–PE gave the desired product (206 mg, 79%).

Pale yellow solid; mp 152–154 °C.

IR (KBr): 3326, 3287, 3238, 3192, 3128, 3058, 3035, 2951, 2867, 2802, 1720, 1548, 1597, 1444, 1230, 1176, 1157, 1120, 694 cm^{-1}.

^{1}H NMR (200 MHz, CD_3OD): δ = 1.48–1.68, 1.84–2.26 (each m, 2 H), 2.50 (dd, ^2J = 13.0 Hz, ^3J = 5.3 Hz, 1 H), 2.58–2.92 (m, 2 H), 2.83 (dd, ^2J = 12.8 Hz, ^3J = 2.5 Hz, 1 H), 3.06–3.26 (m, 1 H), 3.44, 3.73 (each d, ^2J = 13.8 Hz, 1 H), 4.68–4.80 (m, 1 H), 6.94–7.06 (m, 2 H), 7.11–7.65 (m, 14 H), 7.73–7.90 (m, 4 H).

^{13}C NMR (50 MHz, CD_3OD): δ = 26.7, 26.9 (d, J_{PC} = 69.0 Hz), 27.5, 52.0, 55.0, 59.4, 70.3, 120.4, 123.9 (d, J_{PC} = 6.3 Hz), 128.0, 129.3 (2 C), 129.6, 129.7 (each 2 C), 129.9, 130.0 (d, J_{PC} = 11.7 Hz, 4 C), 131.7 (d, J_{PC} = 9.7 Hz, 2 C), 131.8 (d, J_{PC} = 9.7 Hz, 2 C), 133.3 (d, J_{PC} = 2.9 Hz, 2 C), 133.4 (d, J_{PC} = 99.6 Hz), 134.5 (d, J_{PC} = 100.1 Hz), 140.0, 140.2, 155.5.

^{31}P NMR (162 MHz, CD_3OD): δ = 37.1.

Anal. Calcd for $C_{32}H_{33}N_2O_3P$: C, 73.27; H, 6.34; N, 5.34. Found: C, 72.49; H, 6.21; N, 5.64.

***cis*-1-Benzyl-2-(diphenylphosphinylmethyl)-5-(benzyloxy)piperidine (*cis*-12)**

A solution of *cis*-**10f** (2.385 g, 5.89 mmol) in anhydrous THF (74 mL) was cooled to 0 °C and NaH (339.2 mg, 7.07 mmol) was added in small portions. The mixture was allowed to warm to r.t. and stirred for 30 min. Bu_4NI (435 mg, 1.178 mmol) and BnBr (0.77 mL, 6.479 mmol) were added and the resulting mixture was heated at 50 °C for 2 h. The mixture was hydrolyzed with H_2O (4.5 mL), extracted with a mixture of Et_2O–CH_2Cl_2 (2:1, 3 × 5 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column

chromatography (EtOAc–PE–Et_3N, 2:1:2 v/v) afforded the title product (1.784 g, 61%).

Colorless needles; mp 107 °C.

IR (KBr): 3050, 3025, 2945, 2868, 1591, 1495, 1439, 1355, 1180, 1121, 1107, 906, 739, 695 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.40–2.04 (m, 4 H), 2.33 (dd, ^2J = 11.4 Hz, ^3J = 9.8 Hz, 1 H), 2.45 (ddd, ^2J = 12.2 Hz, ^3J = 2.4 Hz, J_{PH} = 14.8 Hz, 1 H), 2.62 (ddd, ^2J = 12.8 Hz, ^3J = 10.0 Hz, J_{PH} = 14.8 Hz, 1 H), 2.74 (dd, ^2J = 11.6 Hz, ^3J = 4.4 Hz, 1 H), 3.27–3.54 (m, 2 H), 3.49 (s, 2 H), 4.41, 4.49 (each d, ^2J = 11.8 Hz, 1 H), 7.12–7.33 (m, 10 H), 7.35–7.55 (m, 6 H), 7.64–7.82 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.8 (d, J_{PC} = 68.9 Hz), 25.7, 27.7 (d, J_{PC} = 1.6 Hz), 50.3, 52.3, 58.6, 70.2, 73.9, 126.9, 127.4 (2 C), 127.5 (2 C), 128.2 (2 C), 128.3 (4 C), 128.6 (d, J_{PC} = 11.9 Hz, 2 C), 130.5, 130.7 (d, J_{PC} = 9.2 Hz, 2 C), 131.6 (d, J_{PC} = 2.4 Hz, 2 C), 132.9 (d, J_{PC} = 98.0 Hz), 134.2 (d, J_{PC} = 100.8 Hz), 138.6, 138.9.

^{31}P NMR (162 MHz, $CDCl_3$): δ = 30.5.

Anal. Calcd for $C_{32}H_{34}NO_2P$: C, 77.55; H, 6.91; N, 2.83. Found: C, 77.47; H, 6.99; N, 2.73.

trans-1-Benzyl-2-(diphenylphosphinylmethyl)-5-(benzyloxy)piperidine (*trans*-12)

In an analogous manner to that described for the synthesis of *cis*-**12**, *trans*-**12** was prepared from *trans*-**10f** (1.450 g, 3.58 mmol) using NaH (206 mg, 4.296 mmol), Bu_4NI (264.5 mg, 0.716 mmol) and BnBr (0.468 mL, 3.938 mmol) in THF (45 mL). Purification by flash column chromatography (EtOAc–PE–Et_3N, 2:1:2 v/v) gave the title product (0.991 g, 56%).

Yellow solid; mp 121 °C.

IR (KBr): 3080, 3058, 3030, 2941, 1591, 1437, 1183, 1121, 1105, 741, 696 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.24–1.58 (m, 2 H), 1.84–1.98 (m, 1 H), 2.19 (dd and m, ^2J = 11.8 Hz, ^3J = 8.0 Hz, 2 H), 2.34 (ddd, ^2J = 12.6 Hz, ^3J = 9.8 Hz, J_{PH} = 15.0 Hz, 1 H), 2.71 (ddd, ^2J = 12.4 Hz, ^3J = 2.6 Hz, J_{PH} = 15.0 Hz, 1 H), 2.82–2.96 (m, 2 H), 3.29 (d, ^2J = 14.0 Hz, 1 H), 3.35–3.50 (m, 1 H), 3.84 (d, ^2J = 13.8 Hz, 1 H), 4.37, 4.43 (each d, ^2J = 12.0 Hz, 1 H), 7.17–7.34 (m, 10 H), 7.38–7.52 (m, 6 H), 7.65–7.80 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.4, 29.1, 31.4 (d, J_{PC} = 70.4 Hz, 1 C), 54.5, 55.4, 58.2, 70.0, 73.1, 126.9, 127.3, 127.4, 128.2 (4 C), 128.5, 128.6 (d, J_{PC} = 11.8 Hz), 128.7 (d, J_{PC} = 11.8 Hz), 130.5, 130.7 (each d, J_{PC} = 9.2 Hz), 131.6, 131.7 (each d, J_{PC} = 2.4 Hz), 133.0 (d, J_{PC} = 98.7 Hz), 134.0 (d, J_{PC} = 99.8 Hz), 138.7, 139.2.

^{31}P NMR (162 MHz, $CDCl_3$): δ = 30.0.

MS (EI, 70 eV): *m*/*z* (%) = 496 (2) $[M + H]^+$, 405 (5) $[M + H - C_7H_7]^+$, 404 (16) $[M - C_7H_7]^+$, 294 (14) $[M - Ph_2PO]^+$, 202 (10) $[Ph_2POH]^+$, 201 (28) $[Ph_2PO]^+$, 91 (100) $[C_7H_7]^+$.

Anal. Calcd for $C_{32}H_{34}NO_2P$: C, 77.55; H, 6.91; N, 2.83. Found: C, 77.31; H, 6.99; N, 2.78.

cis-1-Benzyl-2-(1-propenyl)-5-(benzyloxy)piperidine (*cis*-13)

A solution of *cis*-**12** (1.10 g, 2.22 mmol) in anhydrous THF (23 mL) was cooled to –78 °C. *n*-BuLi (1.53 mL, 1.6 M solution in hexane, 2.442 mmol) was added and the mixture stirred at –78 °C for 15 min. Acetaldehyde (0.138 mL, 2.442 mmol) in anhydrous THF (2 mL) was added slowly. The solution was stirred for 30 min, allowed to warm to 0 °C and then quenched with brine (50 mL). The aq layer was extracted with CH_2Cl_2 (5 × 44 mL) and the combined organic layer dried ($MgSO_4$) and concentrated in vacuo. The crude product was dissolved in anhydrous DMF (89 mL) and NaH (128 mg, 2.664 mmol) was added in small portions. The mixture was heated at 60 °C for 2.5 h. After dissolving the dark brown solution in Et_2O (264 mL), it was washed with 1 M NaOH (3 × 44 mL). The organic layer was extracted with 4% HCl (5 × 88 mL) and the combined aq layer was made alkaline with 2 M NaOH. The aq layer was extracted with Et_2O (5 × 176 mL). The combined organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography (PE–EtOAc–Et_3N, 25:1:10 v/v) to give *cis*-**13** (401 mg, 56%) as a 55:45 mixture of *Z**/*E*-isomers.

Pale yellow oil.

IR (film): 3062, 3027, 2937, 2854, 1604, 1494, 1452, 1102, 1067, 735, 697 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ (55:45 mixture of *Z**/*E*-isomers) = 1.51–1.86 (m, each 4 H), 1.61 (dd, ^3J = 6.6 Hz, ^4J = 1.6 Hz, 3 H), 1.71* (dd, ^3J = 6.2 Hz, ^4J = 1.4 Hz, 3 H), 2.25, 2.28* (each dd, ^2J = 12.0 Hz, ^3J = 3.6 Hz, 1 H), 2.78 (dd, ^2J = 12.0 Hz, ^3J = 6.0 Hz, 1 H), 2.82*–2.90 (m, 2 H), 3.20 (ddd, ^3J = 10.8 Hz, ^3J = 8.0 Hz, ^3J = 3.2 Hz, 1 H), 3.275*, 3.279 (each d, ^2J = 13.6 Hz, 1 H), 3.47–3.55 (m, each 1 H), 3.97, 3.89* (each d, ^2J = 13.6 Hz, 1 H), 4.417, 4.419*, 4.473, 4.477* (each d, ^2J = 12.4 Hz, 1 H), 5.52–5.73 (m, each 2 H), 7.19–7.35 (m, each 10 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ (55:45 mixture of *Z**/*E*-isomers) = 13.3*, 18.0, 27.6, 27.6*, 28.1*, 29.0, 53.1, 53.4*, 56.7*, 59.1*, 59.2, 62.8, 69.8*, 69.8, 72.6*, 72.9, 125.4*, 126.6, 126.7, 127.3, 127.5, 127.5, 128.0, 128.0, 128.2, 128.9, 129.0, 131.5*, 131.7, 139.0, 139.4*.

MS (*Z*-isomer) (EI, 70 eV): *m*/*z* (%) = 280 (2) $[M - C_3H_5]^+$, 230 (3) $[M - C_7H_7]^+$, 215 (7), 186 (7), 160 (7), 124 (9), 91 (100) $[C_7H_7]^+$.

MS (*E*-isomer) (EI, 70 eV): *m*/*z* (%) = 322 (1) $[M + H]^+$, 321 (1) $[M]^+$, 280 (5) $[M - C_3H_5]^+$, 230 (7) $[M - C_7H_7]^+$, 215 (18), 200 (8), 186 (13), 160 (15), 124 (13), 91 (100) $[C_7H_7]^+$.

trans-1-Benzyl-2-(1-propenyl)-5-(benzyloxy)piperidine (*trans*-13)

In an analogous manner to that described for the synthesis of *cis*-**13**, *trans*-**13** was prepared from *trans*-**12** (495 mg, 1 mmol) using *n*-BuLi (0.689 mL, 1.6 M solution in *n*-hexane, 1.1 mmol), acetaldehyde (0.062 mL, 1.1 mmol) in THF (10 mL), and NaH (57.6 mg, 1.2 mmol) in DMF (40 mL). Purification by flash column chromatography (PE–EtOAc–Et_3N, 25:1:10 v/v) gave the title product (182 mg, 57%) as a 55:45 mixture of *E*/*Z**-isomers.

Colorless oil.

IR (film): 3063, 3028, 2936, 2856, 2795, 1604, 1495, 1453, 1098, 736, 697 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ (55:45 mixture of *E*/*Z**-isomers) = 1.17–1.68 (m, each 3 H), 1.51*, 1.52 (each d, ^3J = 5.1 Hz, 3 H), 1.92 (m_c, 2 × each 1 H), 2.00 (m_c, 2 × each 1 H), 2.51 (ddd, ^3J = 10.4 Hz, ^3J = 7.6 Hz, ^3J = 2.8 Hz, 1 H), 2.91* (ddd, ^3J = 10.6 Hz, ^3J = 7.8 Hz, ^3J = 2.8 Hz, 1 H), 2.94, 2.96* (each d, ^2J = 13.6 Hz, 1 H), 3.28–3.36 (m, each 1 H), 3.37–3.47 (m, each 1 H), 4.17*, 4.22 (each d, ^2J = 13.6 Hz, 1 H), 4.21 (each d, ^2J = 11.9 Hz, 1 H), 4.25, 4.26* (each d, ^2J = 11.9 Hz, 1 H), 5.40–5.54 (m, each 2 H), 7.03–7.24 (m, each 8 H), 7.33–7.40 (m, each 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ (55:45 mixture of *E*/*Z**-isomers) = 13.5*, 17.9, 30.6*, 30.7*, 30.7, 31.9, 56.7, 56.8*, 58.7*, 59.2*, 59.3, 65.2, 70.3, 70.3*, 74.7, 74.8*, 125.6*, 126.7, 126.7*, 127.3, 127.4, 127.6, 128.1, 128.3, 129.0, 129.2, 133.9*, 134.7, 138.7, 139.2*.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{22}H_{27}NO$: 321.2093; found: 321.2092.

cis-2-Propyl-5-(benzyloxy)piperidine (14)

Under a H_2 atm, a solution of *cis*-**13** (161 mg, 0.5 mmol) in EtOH (1 mL) was added to a suspension of $Pd(OH)_2/C$ (20 wt%) in EtOH (4 mL). 2 M HCl (5.8 equiv, 1.4 mL) was added slowly and the mixture was stirred for 5 d. After filtration, the catalyst was washed with EtOH. The filtrate was neutralized with 2 M NaOH and evaporated. The residue was taken up in brine (8.5 mL) and the aq layer extracted with $CHCl_3$ (4 × 5 mL). The combined organic layer was dried ($MgSO_4$) and the solvents evaporated. Purification by flash column

chromatography (PE–EtOAc–Et_3N, 25:1:10) gave the title product (65 mg, 56%) as a yellow oil.

IR (NaCl): 3301, 3064, 3031, 2955, 2930, 2869, 1561, 1544, 1497, 1454, 1093, 1070, 736, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, ^3J = 7.2 Hz, 3 H), 1.24–1.60 (m, 7 H), 2.06 (ddddd, ^2J = 13.8 Hz, ^3J = 6.0 Hz, ^3J = 3.0 Hz, ^3J = 3.0 Hz, ^4J = 0.6 Hz, 1 H), 2.28 (br s, 1 H), 2.52 (dddd, ^3J = 9.6 Hz, ^3J = 9.6 Hz, ^3J = 3.2 Hz, ^3J = 3.2 Hz, 1 H), 2.73 (dd, ^2J = 13.6 Hz, ^3J = 1.6 Hz, 1 H), 3.20 (dt, ^2J = 13.6 Hz, ^3J = 2.4 Hz, 1 H), 3.42–3.47 (m, 1 H), 4.52, 4.56 (each d, ^2J = 12.0 Hz, 1 H), 7.25–7.38 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 19.1, 27.4, 28.0, 38.9, 49.3, 55.7, 69.9, 71.1, 127.4, 127.5, 128.3, 138.9

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{23}NO$: 233.1780; found: 233.1780.

***trans*-5-Hydroxy-2-propylpiperidine (Pseudoconhydrine, 5)**

10% Pd/C (15 mg, 17 wt%) was dissolved in anhydrous MeOH (5 mL) and prehydrogenated for 30 min. A solution of *trans*-**13** (86 mg, 0.267 mmol) in anhydrous MeOH (3 mL) and 2 M HCl (1.5 equiv) were added slowly. The mixture was stirred for 4 d at r.t. under H_2. After filtration, the filtrate was neutralized with 2 M NaOH and concentrated in vacuo. Brine (3 mL) was added and the aq layer extracted with $CHCl_3$ (4 × 5 mL). The combined organic layer was dried ($MgSO_4$) and evaporated carefully. Sublimation[11a,j] gave pseudoconhydrine (29 mg, 26%).

Colorless solid; mp 87–89 °C (Lit.[11a] 91.5–92 °C).

IR (KBr): 3292, 3126, 2955, 2921, 2854, 2828, 1449, 1050 cm^{-1}.

^1H NMR (400 MHz, D_2O): δ = 0.85 (br t, ^3J = 7.2 Hz, 3 H), 1.10 (dddd, ^2J = 13.4 Hz, ^3J = 11.2 Hz, ^3J = 11.2 Hz, ^3J = 3.6 Hz, 1 H), 1.23–1.35 (m, 5 H), 1.78 (dq, ^2J = 13.4 Hz, ^3J = 3.4 Hz, 1 H), 1.99 (br d, *J* = 12.0 Hz, 1 H), 2.34 (dd, ^2J = 11.6 Hz, ^3J = 10.6 Hz, 1 H), 2.40–2.49 (m, 1 H), 3.06 (ddd, ^2J = 11.2 Hz, ^3J = 4.2 Hz, ^4J = 2.2 Hz, 1 H), 3.60 (dddd, ^3J = 11.2 Hz, ^3J = 11.2 Hz, ^3J = 4.2 Hz, ^3J = 4.2 Hz, 1 H).

^{13}C NMR (100 MHz, D_2O): δ = 13.8, 19.1, 30.3, 32.9, 37.7, 52.0, 55.0, 67.8.

***trans*-5-Hydroxy-2-propylpiperidine Hydrochloride (5·HCl)**

Anhydrous HCl gas was bubbled through a solution of **5** (10 mg, 0.07 mmol) in $CHCl_3$ (3 mL) for 10 min. The solvent was evaporated and the residue, a pale yellow solid, was crystallized from anhydrous acetone to give **5**·HCl (5 mg, 40%).

Colorless solid; mp 182 °C (Lit.[12p] 185–185.5 °C).

IR (KBr): 3374, 2960, 2939, 2873, 2807, 2508, 1104.

^1H NMR (400 MHz, D_2O): δ = 0.84 (t, ^3J = 7.4 Hz, 3 H), 1.27–1.56 (m, 6 H), 1.97–2.10 (m, 2 H), 2.68 (dd, ^2J = 12.0 Hz, ^3J = 10.8 Hz, 1 H), 2.98–3.10 (m, 1 H), 3.33 (ddd, ^2J = 12.0 Hz, ^3J = 4.6 Hz, ^4J = 1.8 Hz, 1 H), 3.78–3.88 (m, 1 H).

^{13}C NMR (101 MHz, D_2O, with DMSO as an internal standard at δ = 39.51): δ = 13.3, 18.4, 26.4, 30.6, 34.6, 48.6, 56.0, 64.3.

***cis*-5-Hydroxy-2-propylpiperidine (*epi*-5)**

In an analogous manner to that described for the synthesis of pseudoconhydrine (**5**), compound **14** (42 mg, 0.18 mmol) was deprotected under a H_2 atm using 10% Pd/C (6.3 mg) as the catalyst, MeOH (3 mL) and 2 M HCl (0.13 mL, 0.27 mmol). The reaction time was 4 d. The crude product (22 mg, 86%) was characterized spectroscopically without further purification.

IR (film): 3288, 2930, 1440, 1106, 980 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, ^3J = 7.2 Hz, 3 H), 1.28–1.59 (m, 7 H), 1.79–1.91 (m, 1 H), 2.35 (br s, 2 H), 2.44–2.63 (m, 1 H), 2.77 (dd, ^2J = 12.0 Hz, ^3J = 1.6 Hz, 1 H), 3.01 (dt, ^2J = 12.0 Hz, ^3J = 2.8 Hz, 1 H), 3.81–3.90 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 18.9, 27.0, 31.1, 39.1, 52.6, 56.5, 64.4.

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