A Novel Asymmetric Synthesis of *cis*-(3*R*,4*R*)-*N*-(*tert*-Butoxycarbonyl)-4-methyl-3-(methylamino)piperidine

Bao-Yu Hao,[a,c] Jin-Qiang Liu,*[b] Wei-Han Zhang,[c] Xin-Zhi Chen*[a]

[a] Department of Chemical and Biological Engineering, Zhejiang University, Hangzhou 310027, P. R. of China
Fax +86(571)87951615; E-mail: xzchen@zju.edu.cn; E-mail: liuque.zju@hotmail.com

[b] College of Chemistry and Chemical Engineering, Luoyang Normal University, Luoyang 471022, P. R. of China

[c] Hutchison MediPharma Innovation for Health, Shanghai 201203, P. R. of China

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Abstract: *cis*-(3*R*,4*R*)-*N*-(*tert*-Butoxycarbonyl)-4-methyl-3-(methylamino)piperidine, a key intermediate for the synthesis of CP-690550 (a potent protein kinase inhibitor), is prepared via an asymmetric approach starting from ethyl 1-benzyl-3-oxopiperidine-4-carboxylate hydrochloride in an overall yield of 49%. The mild conditions and high yields obtained during the synthesis suggest a potential industrial application for this route.

Key words: asymmetric synthesis, protecting groups, piperidines, protein kinase inhibitor, deoxygenation

CP-690550 (Figure 1), developed by Pfizer, is a potent protein kinase inhibitor (for example, of the enzyme Janus Kinase 3). It can be utilized as an immunosuppressive agent for the treatment of autoimmune disease and in organ transplants.[1]

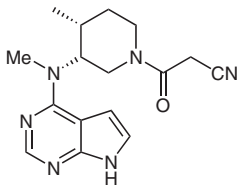
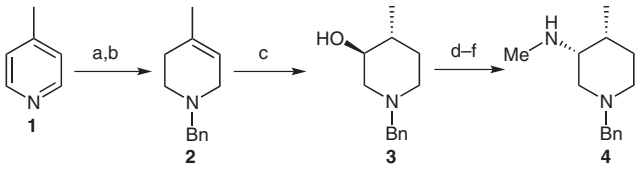


Figure 1 Protein kinase inhibitor CP-690550

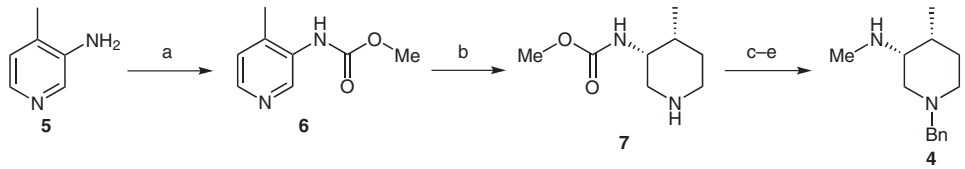


Scheme 1 *Reagents and conditions*: (a) BnCl, acetone, 73%; (b) $NaBH_4$, EtOH, 73%; (c) (i) $BF_3{\cdot}OEt_2$, (ii) BH_3, (iii) MeOH, $CaCl_2$, H_2O, (iv) H_2O_2, (v) NaOH, (vi) TsOH, 88%; (d) $SO_3{\cdot}py$, DMSO, Et_3N; (e) $MeNH_2$, $NaBH(OAc)_3$; (f) HCl, 53% (3 steps).

The heterocyclic compound, *cis*-(3*R*,4*R*)-*N*-(*tert*-butoxycarbonyl)-4-methyl-3-(methylamino)piperidine (**19**) represents a key intermediate in the preparation of CP-690550, and efficient procedures for the asymmetric synthesis of **19** and similar compounds have attracted the attention of medicinal chemists. Routes toward analogues of **19** have been developed including two from Pfizer,[2,3] and another by Jiang.[4] Pfizer's first route started with the benzylation of 4-pipecoline (**1**) followed by reduction with sodium borohydride to afford **2**, which underwent a hydroboration–oxidation sequence to yield hydroxy piperidine **3**. (3*R*,4*R*)-1-Benzyl-4-methyl-3-(methylamino)piperidine (**4**) was obtained after installation of the 3-methylamino moiety via oxidation and reductive amination (Scheme 1).[2] The second route reported by Pfizer involved a four-step transformation starting from 4-methylpyridin-3-amine (**5**) to yield compound **4** as shown in Scheme 2.[3]

Jiang's route[4] provided a method to access all four enantiomers of a *tert*-butoxycarbonyl (Boc) protected analogue of compound **4** (Scheme 3).

All three routes were efficient, particularly those of Pfizer which afforded kilogram quantities of enantiomerically pure **4**. However, there were drawbacks in all three routes. For example, Pfizer's first route[2] (Scheme 1) suffered from the production of dimethyl sulfide during oxidation of the alcohol, required a large volume of solvent during the work-up and isolation of the hydroboration reaction product, and resolution of the diastereomeric final product **4** proved difficult. The second route reported by Pfizer employed a high-cost raw material and a low overall yield was obtained.[3] Furthermore, Jiang's route[4] was too long to industrialize and employed an expensive catalyst which gave a poor product yield. Thus, a new and simple syn-



Scheme 2 *Reagents and conditions*: (a) KO*t*-Bu, $(MeO_2C)_2O$, THF, 61%; (b) Rh/C, AcOH, 75%; (c) PhCHO, $NaBH(OAc)_3$, 68%; (d) $LiAlH_4$, THF; (e) HCl, EtOH, 47%.

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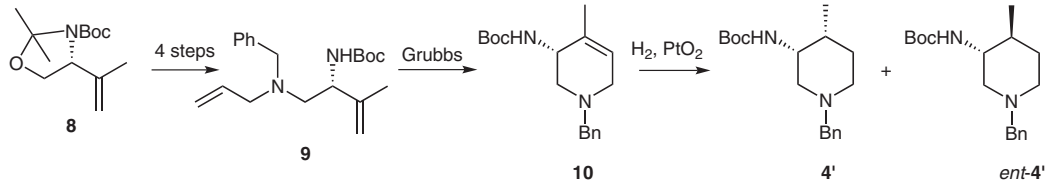
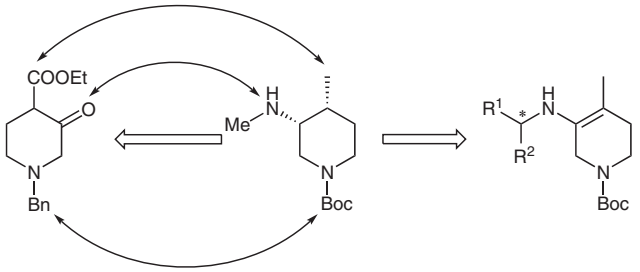


Scheme 3 Jiang's preparation of analogues of compound **4**

thetic procedure toward a compound of type **4** was needed. Herein, we disclose a new route to piperidine **19** (a Boc-protected analogue of **4**) starting from commercially available ethyl 1-benzyl-3-oxopiperidine-4-carboxylate hydrochloride (**11**). As benzyl chloride is a lachrymator, we replaced the benzyl nitrogen protecting group with a *tert*-butoxycarbonyl group.

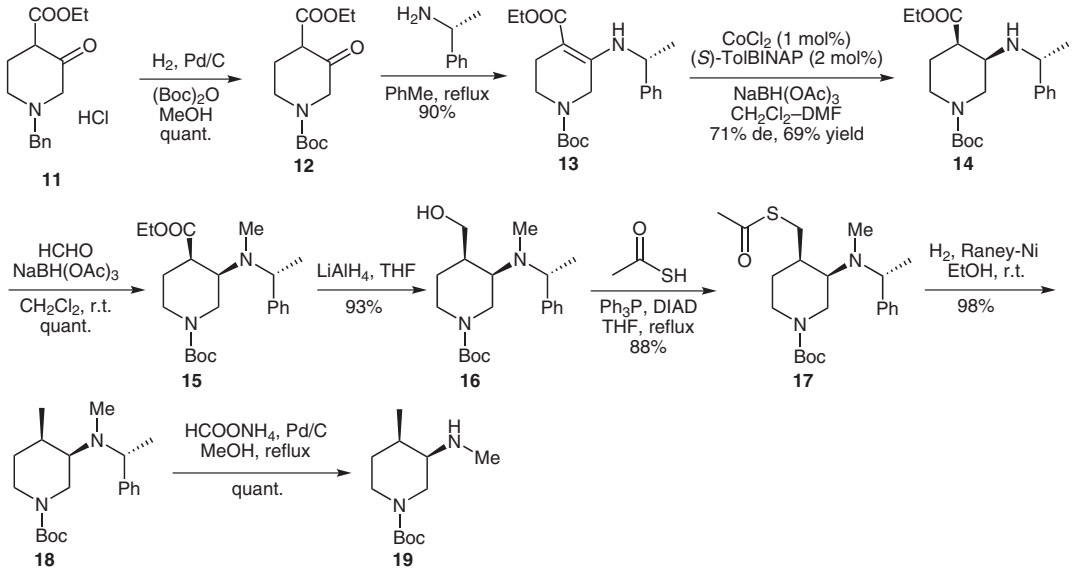
There were three main differences between starting material **11** and the desired product **19**: the nitrogen protecting groups, the carbonyl at C-3 and the ester at C-4 (Scheme 4). Exchange of the nitrogen protecting group was envisaged to be simple and high yielding. The ester carbonyl group was to be replaced by a methyl group through reduction and elimination of a hydroxy group at C-4. Furthermore, conversion of the keto carbonyl into a methylamino group was expected to be realized using a similar procedure to that reported in Pfizer's first route.[2]



Scheme 4 Differences in the structures of compounds **11** and **19**

The installation of the required *cis*-stereochemistry at C-3 and C-4 would necessitate reduction of a C=C double bond which typically forms two *cis*-stereocenters. Thus, to avoid the troublesome resolution experienced by the team at Pfizer, the inclusion of an auxiliary stereocenter was necessary α to the amino nitrogen atom (Scheme 4). We decided to employ (*R*)-α-methylbenzylamine as the auxiliary group as it is commercially available and can be easily removed by reductive elimination. It should be noted that a similar protocol was adopted for the synthesis of an analogue of piperidine **19**.[5] However, the harsh reaction conditions employed made it unsuitable for the industrial-scale synthesis of **19** and hence, optimized conditions were still needed.

The first step in our synthesis of **19** (Scheme 5) required exchange of the benzyl nitrogen protecting group in compound **11** for a *tert*-butoxycarbonyl. A previous report[5] described cleavage of the benzyl group in the same substrate using hydrogen gas (60 psi) in ethanol using palladium hydroxide on carbon [$Pd(OH)_2$/C] as the catalyst. These conditions were too harsh (high hydrogen pressure) and the catalyst too expensive to use on an industrial scale. We found that the same reaction gave a quantitative yield of the desired product at atmospheric hydrogen pressure using palladium on charcoal (5% Pd/C) as the catalyst, in methanol containing di-*tert*-butyldicarbonate (Boc_2O); this procedure should be convenient for industrialization.



Scheme 5 Synthetic route to piperidine **19**

Introduction of the (*R*)-α-methylbenzylamino group would facilitate the synthesis in terms of monitoring the reaction by thin layer chromatography (due to the presence of a fluorescent phenyl moiety) and in product separation. Furthermore, the presence of the chiral center α to the nitrogen atom would make the two enantiomers of **18** diastereomeric, and appropriate chiral induction would give the product with the desired configuration.[5] The reaction between **12** and (*R*)-α-methylbenzylamine proceeded under conditions similar to those described in the literature,[5] but required a shorter time and gave an acceptable yield of amine **13**.

In an effort to make our route more concise, we attempted to transform **12** into ethyl 1-(*tert*-butoxycarbonyl)-3-{[(1*S*)-1-phenylethyl]methylamino}-5,6-dihydropyridine-4(2*H*)-carboxylate (**13′**) (Figure 2) using (1*S*)-*N*-methyl-1-phenylethanamine. Disappointingly however, the amide **20** was obtained (Figure 2). The reason for the formation of compound **20** might be due to the high nucleophilicity of (1*S*)-*N*-methyl-1-phenylethanamine and the high temperature employed. The azeotropic mixture of water–methanol and toluene could result in the removal of water–methanol, and thus shift the equilibrium toward the product resulting in the high yield of **20** obtained. Efforts to prevent this outcome, such as lowering the reaction temperature and using different solvents, failed. Hence, we turned to other methods to synthesize the title compound.

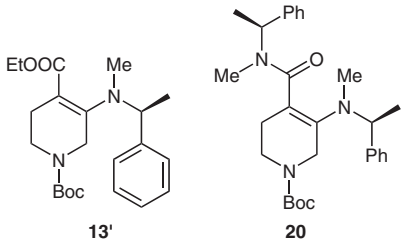


Figure 2 Structures of compounds **13′** and **20**

Methylation of the secondary amine was to follow reduction of the C=C double bond in compound **13** as formation of an intramolecular hydrogen bond between the ester carbonyl and the amine N–H would generate a six-membered ring; this would make the resulting structure more stable than the corresponding N-methylated analogue of **13**. Hydrogenation of **13** should proceed under steric control to give the desired product via attack of the hydrogen from the favored *si* face of the C=C bond as shown in Figure 3.

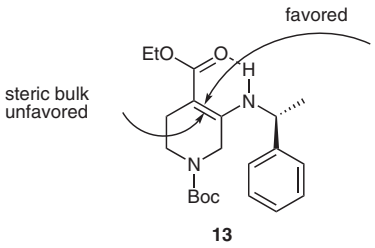


Figure 3 Hydrogenation of compound **13**

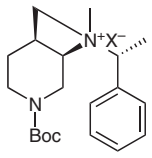
There are numerous methods described in the literature to achieve asymmetric reduction of C=C double bonds.[6] The reported[5] reduction of **13** employed sodium triacetoxyborohydride [$NaBH(OAc)_3$] as the reducing agent and 4 Å molecular sieves as the promoter. Initially, we adopted the same conditions as Frost et al.,[5] but only obtained a poor diastereomeric excess of 40%. To obtain higher selectivity, various metal catalysts including PPh_3RuCl, ruthenium(III) chloride ($RuCl_3$), benzylidene-bis(tricyclohexylphosphine)dichlororuthenium (Grubbs I), ruthenium(III) acetate [$Ru(OAc)_3$], etc., and related chiral phosphorus-containing ligands such as (*R*)-(+)-(1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine) [(*R*)-BINAP], (*S*)-(–)-(1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine) [(*S*)-BINAP], (*R*)-(–)-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethyl di-*tert*-butylphosphine and (1*R*,1′*R*,2*R*,2′*R*)-(–)-2,2′-diphenylphosphino-1,1′-bicyclopentyl [(*R*,*R*)-BICP] were all employed. However, poor yields and diastereomeric excesses were obtained. In contrast, a good yield and diastereomeric excess (71%) of compound **14** were obtained at ambient temperature using the complex formed from cobalt(II) chloride ($CoCl_2$) and (*S*)-(–)-2,2′-*p*-tolyl-phosphino)-1,1′-binaphthyl [(*S*)-TolBINAP] as the catalyst and sodium triacetoxyborohydride as the reducing agent.

The methylation of amines is a well-documented reaction and common reagents for this process include dimethyl sulfate, methyl iodide, dimethyl carbonate [$(MeO)_2CO$], etc. We found that using methyl iodide with potassium carbonate as the base gave poor yields of the desired product **15** despite employing tetrahydrofuran, *N*,*N*-dimethylformamide or acetonitrile as the solvent. The reason for this might be due to the steric bulk at the nitrogen atom. If this was the case, then methylation with formaldehyde could afford the required product. In the event, amine **15** was obtained in quantitative yield at ambient temperature via reaction of **14** with five equivalents of formaldehyde using sodium triacetoxyborohydride as the reductant.

Reduction of esters can be achieved in a straightforward manner with sodium borohydride, diborane or lithium aluminum hydride. However, we found that sodium borohydride was not suitable for this conversion. Lithium aluminum hydride was chosen as the reducing agent as it afforded a high yield of product **16** and the reaction was simple to perform and work up.

The substitution of a hydroxy group for hydrogen has been well documented. Methods include the Barton–McCombie deoxygenation and substitution of the hydroxy group with a halogen followed by reduction. However, these methods proved to be low-yielding in our hands due to the fact they had to be operated at high temperature, and led to the formation of a bicyclo[4.2.0] compound, **21** (Figure 4), which hindered further reaction. Instead, we employed the Mitsunobu reaction for this conversion to give initially intermediate **17**; the bicyclic compound **21** was not formed from **17**, even at high temperature. The

desired transformation was complete after Raney nickel catalyzed hydrogenation of **17** to give substituted piperidine **18**.



21

Figure 4 Structure of bicyclic compound **21**

Removal of the auxiliary benzyl group of **18** to give **19** in quantitative yield was carried out at reflux temperature (the reaction did not proceed at ambient temperature and pressure) in methanol with palladium on charcoal as the catalyst and ammonium formate ($HCOONH_4$) as the hydrogen source.

In conclusion, we have developed an asymmetric route to the synthesis of piperidine **19** which is an important intermediate for the synthesis of the protein kinase inhibitor, CP-690550. The product was obtained in 50% overall yield and in high enantiomeric excess using convenient transformations. The key reaction was the asymmetric hydrogenation of intermediate **13** catalyzed by (*S*)-TolBINAP.

All the reagents were chemical or analytical grade and were purified before use. ^{1}H and ^{13}C NMR spectra were recorded on a Varian AM-400 MHz spectrometer using $CDCl_3$ as the solvent and TMS as the internal standard. The ^{1}H NMR data for compounds **12** and **13** were in agreement with those reported in the literature.[5] LC–MS spectra were obtained using an Agilent Technologies 6120MSD mass spectrometer. HRMS was performed on a Waters Q-TOF spectrometer. HPLC analyses were performed on an Agilent Technologies 1200 Series instrument. TLC analyses were accomplished on Merck silica gel 60 F_{254} plates. Chromatographic purification was accomplished using silica gel (200–300 mesh; Qingdao Haiyang Chemical).

_N_-(*tert*-Butoxycarbonyl)-4-ethyloxycarbonyl-3-oxopiperidine (12)

To an autoclave containing MeOH (70 mL) were added compound **11** (12.0 g, 40.30 mmol), Et_3N (7 mL, 50.73 mmol), Boc_2O (8.97 g, 41.09 mmol) and 10% Pd/C (1.2 g). The air was purged three times with H_2. The progress of the reaction was monitored by TLC (PE–EtOAc–Et_3N, 30:5:1). After 4 h the hydrogenation was deemed complete and the Pd/C was removed by filtration. The filtrate was evaporated under reduced pressure and the residue rinsed with EtOAc (3 × 150 mL). The combined organic phase was washed with H_2O (3 × 100 mL) and brine (3 × 100 mL), dried over Na_2SO_4 and the solvent removed under vacuum to yield the title product **12**.

Light-yellow oil; yield: 10.94 g (100%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.24 (q, *J* = 7.1 Hz, 2 H), 4.03 (s, 2 H), 3.48 (t, *J* = 9.9 Hz, 2 H), 2.33 (t, *J* = 5.6 Hz, 2 H), 1.51 (d, *J* = 14.2 Hz, 1 H), 1.47 (s, 9 H), 1.31 (t, *J* = 7.1 Hz, 3 H).

Ethyl 1-(*tert*-Butoxycarbonyl)-3-{[(1*R*)-1-phenylethyl]amino}-5,6-dihydropyridine-4(2*H*)-carboxylate (13)

A soln of compound **12** (10.94 g, 40.30 mmol) and (*R*)-α-methylbenzylamine (5.37 g, 44.31 mmol) in toluene (100 mL) was heated overnight at reflux temperature. After completion of the reaction, the solvent was removed under reduced pressure. The residue was purified on a reduced-pressure column (EtOAc–PE, 30:1 to 4:1) to afford product **13**.

Light-yellow oil; yield: 13.7 g (91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.01 (m, 5 H), 4.60–4.46 (m, 1 H), 4.19–4.13 (m, 2 H), 4.01–3.90 (m, 1 H), 3.58 (s, 2 H), 3.19–3.07 (m, 1 H), 2.35 (s, 2 H), 1.51–1.17 (m, 16 H).

ESI-MS: *m*/*z* = 374.9 $[M + 1]^+$.

Ethyl (3*R*,4*R*)-1-(*tert*-Butoxycarbonyl)-3-{[(1*R*)-1-phenylethyl]amino}piperidine-4-carboxylate (14)

To a mixture of CH_2Cl_2–DMF (33 mL, 10:1) were added **13** (6.2 g, 16.55 mmol), $CoCl_2 \cdot 6H_2O$ (0.04 g, 0.17 mmol) and (*S*)-TolBINAP (0.23 g, 0.34 mmol). The atm was exchanged three times with N_2 and the soln stirred at r.t. for 1 h. The reaction vessel was placed in an ice-H_2O bath and $NaBH(OAc)_3$ (11.0 g, 51.88 mmol) was added. The resulting mixture was slowly warmed to r.t. and stirred overnight. The reaction progress was monitored by TLC, and following completion was quenched with sat. $NaHCO_3$ soln (20 mL) and stirred for an additional 30 min. The mixture was extracted with EtOAc (3 × 100 mL) and the combined organic phase dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography [H_2O–MeOH, 1:9 to 8:2 (50 min)] to afford compound **14**.

Light-yellow oil; yield: 4.3 g (69%); $[\alpha]_D^{25}$ 18.5 (*c* 0.6, MeOH); de = 71%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.22 (m, 5 H), 4.23–4.17 (m, 2 H), 3.92–3.86 (m, 2 H), 3.15 (s, 1 H), 2.99 (dd, *J* = 13.4, 2.3 Hz, 1 H), 2.89–2.86 (m, 1 H), 2.66–2.62 (m, 1 H), 1.74–1.68 (m, 2 H), 1.51 (s, 2 H), 1.39 (s, 9 H), 1.31 (t, *J* = 7.1 Hz, 3 H), 1.26 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 154.2, 145.0, 127.4, 127.2, 125.9, 125.5, 78.7, 59.4, 53.7, 50.1, 43.7, 27.4, 27.3, 24.5, 22.1, 21.5, 13.3, 13.0.

ESI-MS: *m*/*z* = 376.8 $[M + 1]^+$.

Ethyl (3*R*,4*R*)-1-(*tert*-Butoxycarbonyl)-3-{methyl[(1*R*)-1-phenylethyl]amino}piperidine-4-carboxylate (15)

A CH_2Cl_2 (20 mL) soln of compound **14** (4.3 g, 11.42 mmol) and formaldehyde (1.7 g, 57.10 mmol) under an N_2 atm was stirred for 1.5 h at r.t. The reaction vessel was placed in an ice-H_2O bath and $NaBH(OAc)_3$ (7.3 g, 34.43 mmol) was added, the reaction mixture gradually warmed to r.t. and stirred overnight. The reaction progress was monitored by TLC, and following completion was quenched with sat. $NaHCO_3$ soln (20 mL) and stirred for an additional 30 min. The mixture was extracted with EtOAc (3 × 80 mL) and the combined organic phase dried over Na_2SO_4 and evaporated to afford the ester **15**.

Light-yellow oil; yield: 4.4 g (100%); $[\alpha]_D^{25}$ 12.1 (*c* 0.95, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.19 (m, 5 H), 4.23–4.12 (m, 2 H), 4.07–4.05 (m, 1 H), 3.67–3.51 (m, 3 H), 3.04–2.81 (m, 2 H), 2.12 (s, 3 H), 1.92–1.85 (m, 1 H), 1.76–1.67 (m, 2 H), 1.43 (s, 9 H), 1.34 (d, *J* = 6.8 Hz, 3 H), 1.28 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0, 154.7, 143.5, 128.0, 127.6, 126.6, 79.5, 60.1, 58.4, 57.8, 44.9, 42.3, 40.0, 33.2, 28.4, 25.8, 11.2.

ESI-MS: *m*/*z* = 391.2 $[M + 1]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{34}N_2O_4Na$: 413.2412; found: 413.2416.

(3*R*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-hydroxymethyl-3-{methyl[(1*R*)-1-phenylethyl]amino}piperidine (16)

$LiAlH_4$ (0.4 g, 10.52 mmol) was suspended in anhyd THF (15 mL). The atm was exchanged three times with N_2 and the reaction vessel

placed in an ice-H_2O bath. A soln of **15** (3.5 g, 8.96 mmol) in THF (4 mL) was added and the mixture stirred for 30 min. The reaction progress was monitored by TLC, and following completion was quenched with sat. $NaHCO_3$ soln (20 mL). After stirring for an additional 30 min the mixture was extracted with EtOAc (3 × 50 mL), the combined organic phase dried over Na_2SO_4 and evaporated to afford alcohol **16**.

Light-yellow oil; yield: 2.89 g (93%); $[\alpha]_D^{25}$ –2.5 (*c* 0.55, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.15 (m, 5 H), 4.04 (d, *J* = 7.3 Hz, 2 H), 3.78–3.49 (m, 2 H), 3.43 (dt, *J* = 12.8, 4.6 Hz, 1 H), 3.29 (dd, *J* = 13.3, 8.7 Hz, 1 H), 3.50 (s, 1 H), 2.83 (dt, *J* = 8.5, 4.2 Hz, 1 H), 2.31–2.19 (m, 1 H), 2.14 (s, 3 H), 1.67–1.49 (m, 2 H), 1.36 (t, *J* = 6.1 Hz, 13 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.5, 140.1, 127.5, 127.3, 127.0, 126.7, 126.3, 124.5, 78.8, 63.0, 58.1, 42.1, 40.8, 39.5, 32.5, 29.3, 27.4, 25.5, 12.5.

ESI-MS: *m*/*z* = 348.8 $[M + 1]^+$.

(3*R*,4*R*)-4-(Acetylthiomethyl)-1-(*tert*-butoxycarbonyl)-3-{methyl[(1*R*)-1-phenylethyl]amino}piperidine (17)

PPh_3 (0.6 g, 2.28 mmol) was dissolved in anhyd THF (8 mL), the atm was exchanged three times with N_2 and the reaction vessel was placed in an ice-H_2O bath. Diisopropylazodicarboxylate (DIAD) (0.6 mL, 2.42 mmol) was added and the mixture stirred for 30 min. Next, a soln of **16** (0.58 g, 1.66 mmol) in anhyd THF (5 mL) was added and stirred for 30 min. Then, thioacetic acid (0.2 mL, 2.81 mmol) was added and stirred for 30 min at r.t., then the resulting mixture was heated at reflux temperature overnight. The reaction progress was monitored by TLC, and following completion the mixture was concd under reduced pressure. The residue was purified on a silica gel column (EtOAc–PE, 30:1 to 2:1) to yield compound **17**.

Light-yellow oil; yield: 0.6 g (88%); $[\alpha]_D^{25}$ –8.8 (*c* 1.34, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.18 (m, 5 H), 4.16–3.99 (m, 1 H), 3.53 (s, 1 H), 3.28 (dd, *J* = 13.7, 4.6 Hz, 1 H), 3.04 (dd, *J* = 13.7, 10.2 Hz, 1 H), 2.77–2.67 (m, 1 H), 2.35 (s, 3 H), 2.09 (s, 2 H), 1.73 (dd, *J* = 7.8, 4.0 Hz, 1 H), 1.67 (s, 1 H), 1.59 (s, 1 H), 1.43 (s, 9 H), 1.38 (d, *J* = 6.8 Hz, 3 H), 1.25 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.2, 142.3, 128.0, 127.2, 127.0, 126.7, 125.6, 78.6, 56.9, 42.4, 41.0, 38.9, 36.0, 29.6, 27.4, 26.0, 21.7.

ESI-MS: *m*/*z* = 406.9 $[M + 1]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{34}N_2O_3NaS$: 429.2180; found: 429.2188.

(3*R*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-methyl-3-{methyl[(1*R*)-1-phenylethyl]amino}piperidine (18)

Substituted piperidine **17** (0.4 g, 0.98 mmol) in EtOH (4 mL) was treated with Raney-Ni (catalytic amount). The atm was exchanged three times with N_2 and the mixture stirred for 4 h at r.t. The reaction progress was monitored by TLC, and following completion the Raney-Ni was removed by filtration and the filtrate evaporated under reduced pressure to afford product **18**.

Light-yellow oil; yield: 0.32 g (98%); $[\alpha]_D^{25}$ 14.5 (*c* 0.88, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.20 (m, 5 H), 4.27–3.97 (m, 2 H), 3.78 (s, 1 H), 2.94 (t, *J* = 12.8 Hz, 1 H), 2.48 (dt, *J* = 10.7, 4.2 Hz, 1 H), 2.28 (s, 1 H), 2.01 (s, 3 H), 1.73 (d, *J* = 11.1 Hz, 1 H), 1.66 (d, *J* = 12.6 Hz, 1 H), 1.55–1.52 (m, 1 H), 1.44 (s, 9 H), 1.36 (d, *J* = 6.8 Hz, 3 H), 1.03 (d, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0, 143.4, 127.9, 126.4, 79.4, 59.3, 56.0, 41.5, 32.7, 29.7, 29.4, 28.4.

ESI-MS: *m*/*z* = 332.8 $[M + 1]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{32}N_2O_2Na$: 355.2352; found: 355.2361.

***cis*-(3*R*,4*R*)-*N*-(*tert*-Butoxycarbonyl)-4-methyl-3-(methylamino)piperidine (19)**

Compound **18** (0.2 g, 0.60 mmol) in MeOH (5 mL) was treated with 5% Pd/C (0.05 g) and $HCOONH_4$ (0.2 g, 3.17 mmol). The resulting mixture was heated at reflux temperature for 5 h. The progress of the reaction was monitored by TLC, and following completion the catalyst was removed by filtration and the filtrate evaporated to afford the target product **19**.

Light-yellow oil; yield: 0.14 g (100%); $[\alpha]_D^{25}$ –0.9 (*c* 0.65, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.93–3.82 (m, 1 H), 3.68–3.57 (m, 1 H), 3.41–3.39 (m, 1 H), 3.22 (s, 1 H), 3.07 (s, 1 H), 2.68 (s, 3 H), 2.18–2.14 (m, 1 H), 1.68–1.57 (m, 2 H), 1.46 (s, 9 H), 1.14 (d, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 80.5, 57.8, 53.5, 41.9, 33.2, 31.2, 28.9, 28.3, 23.1.

ESI-MS: *m*/*z* = 229.2 $[M + 1]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{24}N_2O_2Na$: 251.1731; found: 251.1735.

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

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