Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 939–943

TETRAHEDRON: *ASYMMETRY*

The asymmetric synthesis of (3*R*)-*N*-methyl-2-oxo-[1,4′-bipiperidine]-3-acetamide in quantity

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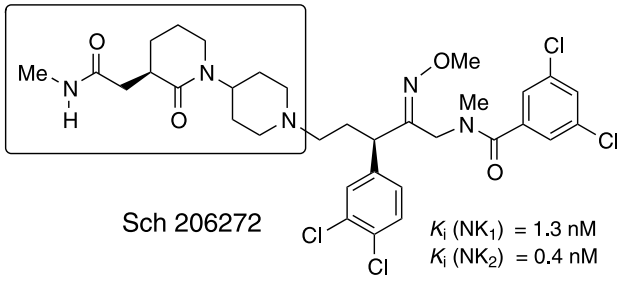
Received 19 December 2001; accepted 29 April 2002

Abstract—The asymmetric synthesis of the enantiomerically pure bipiperidine core fragment of a potent dual NK_1/NK_2 antagonist is described. The utilization of a diastereoselective Michael addition employing Evans' auxiliary as the key step allowed for the preparation of the fragment on a multi-kilogram scale. © 2002 Published by Elsevier Science Ltd.

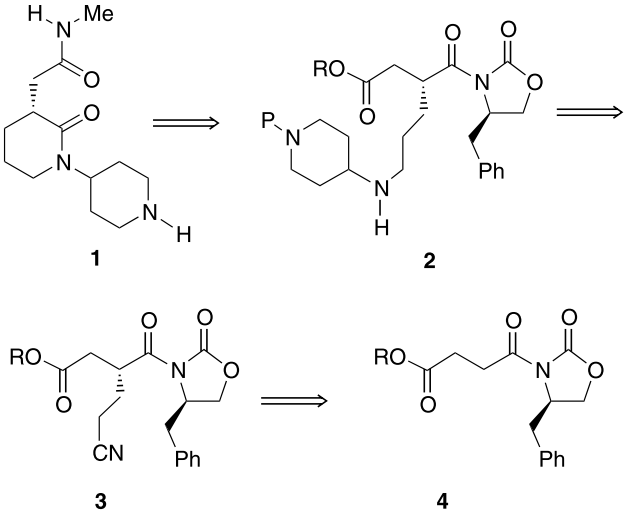
1. Introduction

Structural modification[1] of an oxime lead structure[2] has resulted in the identification of Sch 206272 as a potent dual NK_1/NK_2 antagonist that is quite active in vivo in both guinea pig and dog.[3] As part of our effort to supply multigram quantities for a full preclinical evaluation of Sch 206272, as well as to support the supply of material for toxicological assessment of Sch 206272, an asymmetric synthesis of (3*R*)-*N*-methyl-2-oxo-[1,4′-bipiperidine]-3-acetamide **1** was undertaken. The requirements of the synthesis were that it be short, efficient, amenable to large scale preparation, have minimal chromatographic purification, and provide material with greater than 99% e.e.



2. Retrosynthetic analysis

The retrosynthetic analysis of amino amide **1** centered on simplifying the piperidone ring to the corresponding amino ester **2**. This cyclization would allow for the recovery and reuse of the chiral source. Functional group interchange of the amine back to the nitrile permitted the utilization of methodology developed by Evans and co-workers,[4] wherein the desired stereocenter is constructed by means of a diastereoselective Michael addition of the enolate of **4** to acrylonitrile. We report herein the successful application of this robust methodology to prepare **1** on multi-kilogram scale.



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PII: S0957-4166(02)00229-X

3. Synthesis

Reaction of 3-carbomethoxypropionyl chloride with the lithium salt of (*R*)-4-benzyl-2-oxazolidinone at −78°C provided **6** as a colorless solid in 96% yield after recrystallization from hot isopropanol. Subsequent formation of the enolate of **6** with Ti(O*i*Pr)Cl_3 and diisopropylethylamine at 0°C for 1 h followed by the Michael addition of acrylonitrile[5] at 0°C for 20 h provided pure nitrile **9** as a colorless crystalline solid in 60% yield (>99.5:0.5 d.r.) after recrystallization. The absolute configuration of **9** was confirmed by X-ray crystallographic analysis (Fig. 1, Scheme 1).

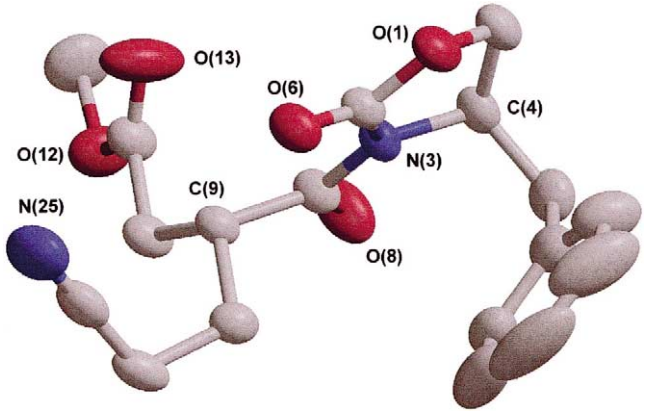
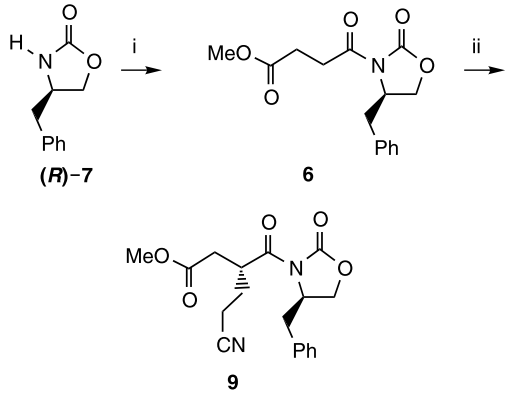
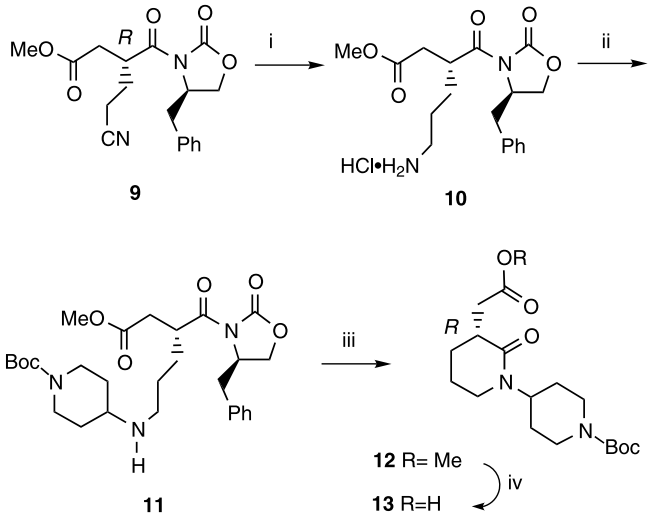


Figure 1. ORTEP drawing of **9**.



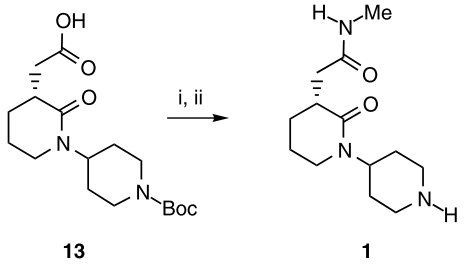
Scheme 1. *Reagents and conditions*: (i) *n*-BuLi, 3-carbomethoxypropionyl chloride, 96%; (ii) Ti(O*i*Pr)Cl_3 and diisopropylethylamine, 0°C, 1 h, acrylonitrile, 20 h, recrystallize in hot isopropanol, 60% yield.

Hydrogenation of the nitrile **9** with 5% PtO_2 in MeOH/$CHCl_3$ at 45 psi provided clean reduction to the desired amine hydrochloride, however, some reduction (17%) of the phenyl to cyclohexyl on the chiral auxiliary was noted. In an effort to adapt this procedure to kilo-scale, as well as minimize the problematic auxiliary reduction, various solvents, catalysts and catalyst loads were screened. It was found that by hydrogenation of **9** at 60 psi in THF with 40 wt% of 5% Pt/C (50% wet) and *p*-toluene sulfonic acid as a proton source, provided clean reduction of the nitrile with minimal reduction of the auxiliary phenyl ring. Reductive amination of amine hydrochloride **10**[6] with *N*-Boc-4-piperidone in THF utilizing sodium triacetoxyborohydride provided the crude secondary amine **11**. Cyclization of crude **11** in acetonitrile at 50°C for 72 h resulted in conversion to lactam **12**. Optimization of the cyclization of **11** to **12** for large scale was achieved in toluene at reflux for 5 h. The methyl ester **12** was then saponified cleanly with NaOH in toluene at 23°C. The resulting carboxylate salt was separated from the auxiliary by extraction and isolated by acidification, crystallization and filtration to provide the pure protected amino acid **13** (99% e.e.) as a white powder in 51–67% overall yield from **9** (Scheme 2).



Scheme 2. *Reagents and conditions*: (i) H_2 (60 psi), 5% Pt/C (50% wet), *p*-TSA, THF, 24 h; (ii) *N*-Boc-4-piperidone, THF, -H_2O by azeotropic distillation, then sodium triacetoxyborohydride, 2 h; (iii) toluene, 110°C, 5 h; (iv) NaOH, toluene, 23°C, 16 h, 51–67% yield from **9**.

Subsequent coupling of enantiomerically pure **13** with methylamine using isobutylchloroformate followed by deprotection of the piperidine nitrogen with trifluoroacetic acid proceeded cleanly to **1** without racemization (Scheme 3).



Scheme 3. *Reagents and conditions*: (i) triethylamine, isobutylchoroformate, $MeNH_2$, THF, −20°C; (ii) trifluoroacetic acid, THF, 82% yield from **13**.

4. Summary

Thus, the asymmetric synthesis of (3*R*)-*N*-methyl-2-oxo-[1,4′-bipiperidine]-3-acetamide **1** proceeds in 24–32% overall yield over eight steps with no

chromatography. The synthesis met our initial criteria for being short, efficient, amenable to scale-up (over 10 kg of **1** was prepared using this route), having minimal chromatographic separation, and providing material of >99% e.e.

5. Experimental

5.1. Synthesis of (4*R*)-3-oxazolidinebutanoic acid, γ,2-dioxo-4-(phenylmethyl)-, methyl ester 6

A solution of (*R*)-(+)-4-benzyl-2-oxazolidinone **7** (100 g, 563 mmol) and 1,10-phenanthroline (10 mg) in dry THF (1.25 L; Aldrich Sure Seal) was cooled to −78°C. *n*-BuLi (1.6 M in hexane, 350 mL, 350 mmol, 1 equiv.) was added (via addition funnel at a rate such that the internal temperature remained ≤ -70°C) until the reaction turned brown from the phenanthroline complex (ca. 349.5 mL). After 15 min, 3-carbomethoxypropionyl chloride (69.5 mL, 564 mmol, 1 equiv.) was added over 10 min via syringe (the dark brown color of the reaction mixture fades to light yellow with the first drop of acid chloride). The mixture was stored for 17 h at −78°C for convenience (reaction is complete after 15 min). The reaction mixture was allowed to warm to room temperature then poured into EtOAc (2.5 L)/saturated aqueous NH_4Cl (1 L). The organic layer was washed with saturated aqueous NH_4Cl (1 L), satd $NaHCO_3$ (2.5 L), brine (2.5 L), dried ($MgSO_4$) and concentrated to give the crude product as a yellow solid. Recrystallization from hot isopropanol (820 mL) provided pure product **6** as a colorless crystalline solid (157.9 g, 542 mmol, 96%), mp 90–92°C. TLC (hex/EtOAc, 1:1): R_f sm 0.3 uv, R_f prod 0.6 uv; stain: 5% ethanolic phosphomolybdic acid (pma). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.66–2.77 (m, 1H), 3.20–3.26 (m, 1H), 3.68 (s, 3H), 4.13–4.20 (m, 1H), 4.14 (dd, $J=2.9$, 9.1 Hz, 1H), 4.18 (t, $J=8.4$ Hz, 1H), 4.62–4.65 (m, 1H), 7.16–7.31 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.1, 29.9, 36.7, 50.9, 54.1, 65.3, 126.3, 127.9, 128.4, 134.1, 152.4, 170.8. HRMS calcd for $C_{15}H_{18}NO_5$ $(M+H)^+$ 292.1185, found 292.1195.

5.2. Synthesis of (β*R*,4*R*)-3-oxazolidinebutanoic acid, β-(2-cyanoethyl)-γ,2-dioxo-4-(phenylmethyl)-, methyl ester 9

A solution of $TiCl_4$ (419 mL of 1 M in CH_2Cl_2, 419 mmol) in dry CH_2Cl_2 (1.35 L, Aldrich Sure Seal) was cooled to 0°C and treated with Ti(O*i*-Pr)$_4$ (41.4 mL, 140 mmol) via syringe. After 10 min at 0°C, diisopropylethylamine (102.4 mL, 587 mmol, Aldrich Sure Seal) was added via dry addition funnel (vacuum anhydrous cannula transfer to dry addition funnel). After stirring the resulting dark brown solution for 15 min, oxazolidinone **6** (163.2 g, 561 mmol) was added in one portion. The solution was stirred for 1 h at 0°C whereupon freshly distilled acrylonitrile (147 mL, 2.24 mol) was added via dry addition funnel (vacuum anhydrous cannula transfer to dry addition funnel). The resulting mixture was allowed to stand at 4°C for 18 h. The reaction mixture was poured into 25% aqueous NH_4Cl (4 L)/EtOAc (6 L). The resulting organic layer was washed with 12.5% aqueous NH_4Cl (2×4 L), followed by saturated aqueous $NaHCO_3$ (4 L), brine (4 L), then dried ($MgSO_4$) and concentrated. Trituration of the crude product with diethyl ether (875 mL) and recrystallization from hot methanol (4 mL/g; decolorize with charcoal/silica gel (5 g/2.5 g) if needed) provided the pure product **9** as a colorless crystalline solid (116.5 g, 338.3 mmol, 60%), mp 103–105°C. TLC (hex/EtOAc, 1:1): R_f sm 0.6, R_f prod 0.5; stain: pma. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.92 (m, 1H), 2.12 (m, 1H), 2.44 (t, $J=7.8$ Hz, 2H), 2.55 (dd, $J=4.4$, 17.0 Hz, 1H), 2.81 (dd, $J=9.77$, 13.56 Hz, 1H), 2.93 (dd, $J=10.4$, 17.0 Hz, 1H), 3.32 (dd, $J=3.78$, 13.56 Hz, 1H), 3.68 (s, 3H), 4.16 (m, 1H), 4.23 (dd, $J=2.52$, 8.83 Hz, 1H), 4.30 (t, $J=8.83$ Hz, 1H), 4.72 (m, 1H), 7.21 and 7.36 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 14.3, 26.6, 34.2, 37.2, 37.4, 51.0, 54.5, 64.8, 65.7, 117.8, 126.5, 128.0, 128.4, 134.0, 152.4, 170.8, 172.7. HRMS calcd for $C_{18}H_{21}N_2O_5$ $(M+H)^+$ 345.1450, found 345.1460.

5.3. Synthesis of (3*R*)-1′-[(1,1-dimethylethoxy)carbonyl]-2-oxo-[1,4′-bipiperidine]-3-acetic acid 13

Method A: A solution of nitrile **9** (25 g, 72.6 mmol) in $CHCl_3$ (100 mL) in a 2 L Parr bottle was diluted with MeOH (400 mL) and treated with PtO_2 (1.25 g) and placed on the Parr shaker @ 45 psi. After 24 h the mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The resulting crude amine·HCl (28.3 g) was used in the next step without further purification. TLC (hex/EtOAc, 1:1): R_f sm 0.5 uv, R_f prod 0.0 uv; stain: pma. A solution of the crude amine·HCl **10** (72.6 mmol) was dissolved in 1,2-dichloroethane (500 mL) and treated with HOAc (6 mL, 105 mmol, 1.4 equiv.) followed by *N*-Boc-4 piperidone (14.6 g, 73.5 mmol, 1.01 equiv., Lancaster) followed by $NaB(OAc)_3H$ (25.7 g, 122 mmol, 1.7 equiv.) After stirring for 1.0 h, the crude mixture was poured into a 4 L separatory funnel charged with CH_2Cl_2 (1.4 L). Saturated aqueous $NaHCO_3$ (560 mL) was added carefully. The aqueous layer was removed and the organic layer washed again with saturated aqueous $NaHCO_3$ (560 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The crude **11** (39.1 g) was used in the subsequent cyclization step without further purification. TLC (EtOAc/MeOH, 95:5): R_f sm 0.0 uv, R_f prod 0.25 uv; stain: pma. A solution of the crude amine **11** (72.6 mmol) in acetonitrile (500 mL) was warmed to 50°C. The resulting solution was stirred for 72 h, whereupon it was cooled and concentrated in vacuo. The resulting crude lactam **12** (39.3 g) was used in the following hydrolysis without further purification. TLC (EtOAc/MeOH, 95:5): R_f sm 0.25, R_f prod 0.75; TLC (hex/EtOAc, 1:1): R_f sm 0.0 uv, R_f prod 0.2 non uv, phenyl oxazolidinone 0.4 uv, cyclohexyl oxazolidinone 0.6 non uv; stain: pma. A solution of the crude lactam **12** (39.3 g) (containing up to 72.6 mmol of a mixture of *N*-benzyl and *N*-methyl-cyclohexyl oxazolidinones) in MeOH (150 mL), was treated with NaOH (148 mL of 1N aqueous NaOH, 2.2 equiv.). After stirring for 6 h at 23°C, methanol was removed in vacuo and the resulting solution was diluted with water

(50 mL) and washed with EtOAc (3×200 mL) to remove the oxazolidinone. The aqueous layer was then acidified to pH 2 with 15% aq. HCl (4.4 M, 40 mL). The product was extracted with CH_2Cl_2 (4×200 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated to give the pure acid as a colorless foam (22.3 g, 65.5 mmol, 96% e.e.). Recrystallization from hot acetone (18 mL/g reflux, filter, cool, remove ca. 300 mL solvent on rotovap, seed and sonicate, cool to 10°C, isolate by filtration with 50 mL cold acetone wash) to give the pure product **13** as a colorless solid (16.5 g, 48.5 mmol, 67% from **9**), mp 145–147°C, >99% e.e. by chiral HPLC: Daicel CHIRALCEL® OD column, 85:15 hexane/isopropanol with 0.1% TFA; t_R *R* isomer = 9.5 min; t_R *S*-isomer = 11.3 min. TLC (EtOAc/MeOH, 95:5 w/2% HOAc): R_f sm 0.70, R_f prod 0.55; stain: pma. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (s, 9H), 1.45–1.62 (m, 4H), 1.70–1.78 (m, 1H), 1.86–2.02 (m, 2H), 1.86–2.02 (m, 1H), 2.43 (dd, J = 2.3, 15.4 Hz, 1H), 2.64–2.8 (m, 4H), 3.12 (dd, J = 4.7, 10.5 Hz, 1H), 3.15 (dd, J = 4.5, 10.6 Hz, 1H), 3.20–3.25 (m, 1H), 4.17 (br s, 2H), 4.54–4.62 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.2, 26.4, 27.4, 27.5, 37.2, 37.3, 41.1, 50.7, 78.8, 153.6, 171.8, 173.4. HRMS calcd for $C_{17}H_{29}N_2O_5$ $(M+H)^+$ 341.2076; found 341.2082.

Method B: Compound **9** (120 g, 348 mmol) and *p*-toluene sulfonic acid (72 g, 378 mmol) were dissolved in THF (1.2 L) at 20–25°C under stirring. Platinum (48 g, 5% on charcoal, 50% water wet) was suspended in 55 mL water and added. The suspension was hydrogenated at 20–25°C in an autoclave at 4–5 bar for about 10 h. After complete conversion (followed by HPLC: column: Prodigy 5µ, ODS Phenomenex, 250× 4.6 mm, eluent: acetonitrile/buffer (0.05 M decanesulfonic acid, pH 3) 40/60) the catalyst was removed by filtration (contains compound **10** and the cyclohexyl derivative in a ratio of 9:1) and the filtrate was used without further purification. The filtrate (1.4 L, contains 181 g, 348 mmol compound **10** by theory) was added to *N*-Boc-4-piperidone (70 g, 351 mmol) and the resulting clear solution was concentrated at 40°C/100 mbar to 275 mL. Dry THF (1.8 L) was added and the water content was determined by Karl Fisher titration. Subsequent reduction of the Schiff-base of compound **11** was then initiated if the water content was <0.15% (if the water content >0.15%, the concentration/dilution with dry THF was repeated). The solution was concentrated to 300 mL (contains compound **11**, 184 g by theory, 348 mmol) and added to a solution of sodium triacetoxyborohydride (118 g, 558 mmol) in dry THF (720 mL) over 20 min keeping the temperature at 20–30°C. After complete reaction (followed by HPLC: column: Prodigy 5µ, ODS Phenomenex, 250×4.6 mm, eluent: acetonitrile/buffer (0.05 M decanesulfonic acid, pH 3) 40/60, reaction time: 90 min) water (550 mL) was added over 10 min at 20–25°C. The reaction mixture was concentrated at 40°C/60 mbar to a volume of 600 mL and toluene (1.8 L) was added. The phases were separated and the organic phase was washed twice with an aqueous solution of potassium carbonate and once with an aqueous solution of ammonium chloride. The organic phase was then concentrated at 60°C/60 mbar to a volume of 850 mL (contains **11**, 185 g by theory, 348 mmol), divided into two portions and used in the next step without further purification: half of the toluene solution from the previous step was heated to reflux (about 110°C) and the progress of the ring closure reaction was followed by HPLC (column: Prodigy 5µ, ODS Phenomenex, 250×4.6 mm, eluent: acetonitrile/buffer (0.05 M decanesulfonic acid, pH 3) 40/60, reaction time: 5 h). After complete conversion the reaction mixture was cooled to 20–25°C and used in the next step without further purification/work-up. Sodium hydroxide (conc. 30% in water, 45 mL, 843 mmol) dissolved in water (600 mL) was added to the toluene solution from the previous step at 20–25°C and the resulting mixture was stirred at that temperature for 16 h. After complete conversion (followed by HPLC: column: Prodigy 5µ, ODS Phenomenex, 250×4.6 mm, eluent: acetonitrile/buffer (0.05 M decanesulfonic acid, pH 3) 40/60) water (110 mL) was added and the phases were split. The aqueous phase was extracted with isopropyl acetate (900 mL) and the combined organic phases (toluene and isopropyl acetate phase) were kept for recovery of (*R*)-(+)-4-benzyl-2-oxazolidinone **7** (see note 1). The pH of the water phase was adjusted to 1 to 2 by the addition of HCl (200 mL, 12% in water) during which compound **13** precipitated. Isopropyl acetate (900 mL) was added and the precipitate was dissolved by heating the mixture to 40–45°C. The reaction mixture was cooled to 25–30°C, the phases were split and the water phase was discarded. The organic phase was filtered through a filter aid (Hyflo, 4 g), concentrated to a volume of 360 mL, cooled to −10 to −5°C and stirred at that temperature for 1 h. The product was isolated by filtration, washed with isopropyl acetate (50 mL) and dried in a vacuum oven at 40–45°C until dry to provide 30.5 g of **13** (89.4 mmol, 51% based on compound **9**), HPLC-assay: 99.2% versus std., 99.2% by area; enantiomeric purity (HPLC): 99% (*R*-isomer).

Note 1: Recovery of (*R*)-(+)-4-benzyl-2-oxazolidinone: 2 L of organic phase (contains 49.3 g (*R*)-(+)-4-benzyl-2-oxazolidinone **7**, 278 mmol) was concentrated at 50°C/40 mbar as completely as possible. The resulting residue was dissolved in isopropyl acetate (73 mL) at 20–25°C and *n*-heptane (124 mL) was added over 25 min to the solution. The resulting suspension was cooled to between 0 and 5°C and stirred at that temperature for 1 h. The product was isolated by filtration, washed with *n*-heptane (10 mL) and dried at 40–45°C to give 23 g (46%); HPLC-assay: 98.8% versus satd, 99.6% by area; enantiomeric purity (HPLC): >99.5% of (*R*)-(+)-4-benzyl-2-oxazolidinone.

5.4. Synthesis of (3*R*)-[2-(methylamino)-2-oxoethyl]-2-oxo-[1,4′-bipiperidine]-1′-carboxylic acid, 1,1-dimethylethyl ester 14

A mixture of **13** (1000 g, 2.94 mol) in dry THF (3.5 L) and triethylamine (500 mL, 3.6 mol) was heated to 45°C to dissolve and then cooled to between −40 and −60°C. Ethyl chloroformate (320 mL, 3.3 mol) was then added keeping the temperature below −35°C. The solution was stirred for 30 min whereupon methylamine

(2 M in THF, 2.2 L, 4.4 mol) was added, keeping the temperature under −20°C. Water (1.0 L) was added and the THF was removed by distillation at 40°C under vacuum. The oil remaining was then extracted into ethyl acetate (1×2 L, 1×1 L). The combined ethyl acetate layers were washed with saturated sodium bicarbonate (1×200 mL) and allowed to separate overnight. The ethyl acetate was separated and then the solution was concentrated under vacuum at 40°C to give an oil. Methyl *t*-butyl ether (MTBE, 2.5 L) was then added and the solution was heated to 55°C, seeded, and cooled to 0–5°C for 1 h. The crystalline product was filtered, washed with MTBE (1×500 mL) and dried under vacuum overnight at 40°C to yield a colorless crystalline solid (950 g, 2.69 mol, 91.4%, e.e. >98%), mp 120–122°C. $[\alpha]_D^{23}$ +30.0 (*c* 0.5, methanol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 (s, 9H), 1.48–1.58 (m, 5H), 1.80–1.86 (m, 1H), 1.95–2.02 (m, 1H), 2.69 (m, 1H), 2.37 (dd, $J=4.9$, 14.3 Hz, 1H), 2.57–2.73 (m, 4H), 2.75 (d, $J=5.1$ Hz, 3H), 3.10–3.21 (m, 2H), 4.17 (brs, 2H), 4.43–4.61 (m, 1H), 6.62 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.7, 26.6, 27.3, 28.8, 29.0, 39.3, 39.7, 42.1, 51.3, 80.0, 154.9, 172.6, 172.9. HRMS calcd for $C_{18}H_{32}N_3O_4$ $(M+H)^+$ 354.2393; found 354.2398.

5.5. Synthesis of (3*R*)-*N*-methyl-2-oxo-[1,4′-bipiperidine]-3-acetamide 1

A suspension containing **14** (650 g, 1.84 mol) in toluene (1.4 L) was heated at 55–60°C until all the solids were dissolved. This warm solution was then added to a mixture containing trifluoroacetic acid (1.43 L, 18.6 mol) and toluene (1.2 L), preheated to 55–60°C. During the addition, the temperature was maintained at 55–60°C, and instant gas evolution was observed. After complete addition, the reaction mixture was stirred for another 15 min. HPLC analysis [YMC Pack ODS-A (250×4.6 mm); 0.025% TFA in water/acetonitrile 65/35; flow: 1.0 mL/min; detection: 215 nm; t_R **14** 11.9 min; t_R **1**, 3.5 min] showed that the reaction was complete (>99%). After cooling the reaction mixture to about 20°C, the mixture was concentrated under reduced pressure. The internal temperature was kept below 60°C. The concentrate was diluted with THF (1.2 L), and added to a suspension of $KHCO_3$ (1.43 kg, 14.3 mol) in THF (1.2 L) while maintaining the internal temperature at about 25°C (the neutralization was endothermic). The suspension was filtered, and the collected inorganic salt was washed with THF (300 mL). A solution assay showed that the THF solution contained 415 g (1.64 mol, 89%) of (3*R*)-*N*-methyl-2-oxo-[1,4′-bipiperidine]-3-acetamide **1**. Chiral HPLC assay showed this material to be >99% e.e. [CHIRALCEL® OD (250×4.6 mm); 92% hexane, 8% ethanol, 0.1% TFA, 0.15% water; flow: 2.0 mL/min; temperature: 30°C; detection: 210 nm; t_R (*R*)-**14**, 19.9 min; t_R (*S*)-**14**, 18.1 min]. $[\alpha]_D^{23}$ +32.6 (*c* 0.2, methanol, oxalate salt) ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.55 and 2.00 (m, 2H), 1.62 (m, 2H, H), 1.75 and 1.84 (m, 2H), 2.39 and 2.61 (m, 2H), 2.69 (m, 1H), 2.73 and 3.16 (m, 2H), 2.77 (3H), 3.21 (m, 2H), 4.54 (m, 1H), 6.6 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.4 (C), 26.2, 27.1, 29.6, 39.2, 39.4, 41.7, 45.9, 51.0, 172.2, 172.7. HRMS calcd for $C_{13}H_{24}N_3O_2$ $(M+H)^+$ 254.1869; found 254.1868.

Acknowledgements

The authors thank Dr. Neng-Yang Shih, Dr. John Piwinski and Dr. David Andrews for helpful discussions. Additionally, the authors thank Dr. Corey Strickland and Mr. Cheng Wang for their help in preparing the manuscript.

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