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General and efficient synthetic approach to novel tricyclic spiroketones

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ABSTRACT

A general and efficient synthetic approach to tricyclic spiroketones of interest as useful scaffolds in drug discovery was developed. Starting from commercially available benzyl 4-oxo-1-piperidinecarboxylate (**5**), spirocyclic tetralone **4**, spirocyclic indanone **14**, and spirocyclic benzocycloheptanone **15** were synthesized via six reaction steps in excellent overall yield.

1. Introduction

Privileged structures represent molecular frameworks endowed with inherent affinity for diverse biological receptors or enzymes. Since its introduction by Evans and collaborators[1] describing 1,4-benzodiazepine-2-ones, the term privileged structures has appeared in the literature multiple times and includes structures as diverse as 1,4-dihydropyridines, benzyl-piperidines, and cyclic peptides. With the advent of high throughput screening in drug discovery, there has been significant interest in the incorporation of structural features (substructures or scaffolds) of privileged structures in the design of chemical libraries. It has been shown that biological activity and specificity of compounds based on privileged structures can be modulated with relatively minor changes in the nature of the substituents. The spiro(chromane-2,4′-piperidine), shown in Figure 1, is an example of a privileged structure. Indeed this molecular framework has been used as a core template to design ligands binding to various molecular targets (Fig. 1).[2–8] We recently reported the discovery of novel delta opioid receptor agonists containing as central template the spiro(chromene-2,4′-piperidine) motif. The lead representative in this series (ADL5859) has been recently advanced to Phase II proof of concept studies for the management of pain.[8]

Compound **1**, {*N*,*N*-diethyl-4-(spiro[chromene-2,4′-piperidine]-4-yl)benzamide}, prototypical molecule in this series, was previously identified as a potent delta agonist, displaying excellent selectivity (>1000-fold) for delta over mu and kappa opioid receptors.[8] As part of the lead optimization campaign around this new series of delta opioid agonists, we investigated the bioisosteric replacement of the oxygen atom of the spirocyclic scaffold of **1** with a methylene moiety (compound **2**, Fig. 2). The scaffold **3**, prepared by simply heating a mixture of *N*-Boc-4-piperidone and 2-hydroxyacetophenone in the presence of pyrrolidine[8,9] or L-proline,[10] was used as key intermediate for the synthesis of **1**.[8] Similarly, we envisioned to prepare **2** from the corresponding *N*-protected spirocyclic tetralone **4** (Fig. 2). However, the synthesis of **4** has never been reported. Such spirocyclic ketones are also expected to serve as useful scaffolds for constructing ligands for other biological targets. Therefore, we sought to develop a general method to prepare this novel spirocyclic tetralone system. This article describes a general and efficient synthetic approach to **4**, and the related five-membered ring spirocyclic indanone and the seven-membered ring spirocyclic benzocycloheptanone.

2. Results and discussion

It was speculated that the spirocyclic ring system of **4** could be constructed via the intramolecular Friedel–Crafts acylation reaction on an appropriate piperidine-4-acetic acid derivative. Scheme 1 illustrates our initial synthetic approach to the spirocyclic tetralone **4**. Condensation of commercially available benzyl 4-oxo-1-piperidinecarboxylate (**5**) with ethyl cyanoacetate in the presence of acetic acid and ammonium acetate with azeotropic removal of water formed during the reaction using a Dean–Stark apparatus gave the unsaturated ester **6** in good yield (88%).[11] Compound **6** was subjected to conjugate addition by reaction with organocuprate reagents derived from benzylmagnesium chloride (4 equiv) and copper(I) cyanide (2 equiv) to afford the cyanoester **7** in quantitative yield. Decarboxylation of **7** by treatment with sodium chloride in dimethylsulfoxide containing a small amount of water at 160 °C afforded nitrile **8** in nearly quantitative yield. Conversion of the nitrile functional group in **8** to the corresponding methyl ester by treatment with methanol, in the presence of concentrated sulfuric acid, was incomplete even after refluxing for 3 days and during the reaction the Cbz protecting group was also cleaved. After reprotection of the piperidine amino group with Cbz by treatment with benzyl chloroformate, and subsequent purification by flash

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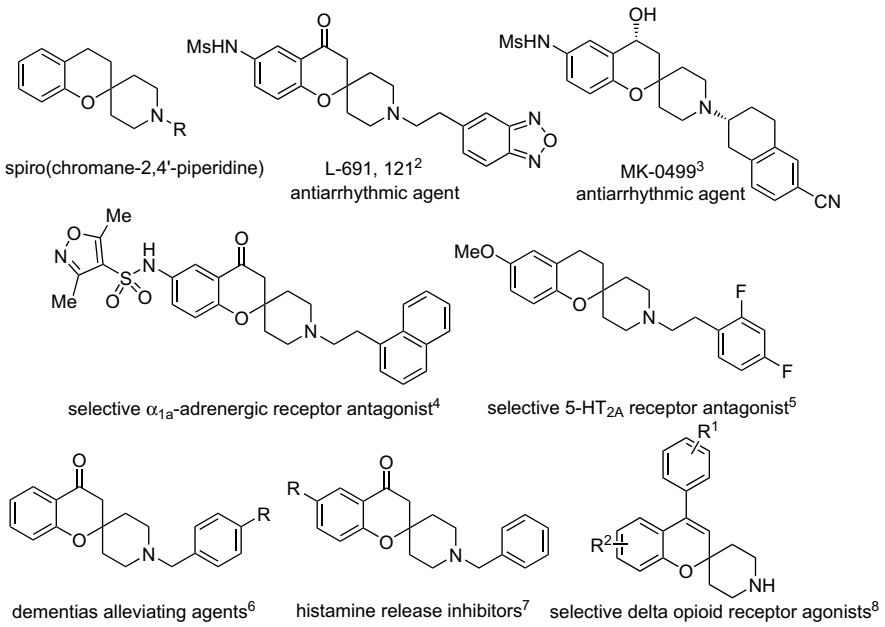


Figure 1. Spiro(chromane-2,4′-piperidine) as a privileged structure in drug discovery.

chromatography, methyl ester **9** was obtained in ~50% yield with recovery of ~35% of nitrile **8**. Ester **9** was then hydrolyzed with lithium hydroxide to furnish the key intermediate carboxylic acid **10** in nearly quantitative yield. Treatment of acid **10** with oxalyl chloride gave the acyl chloride, which was reacted with aluminum chloride to yield, as expected, the intramolecular Friedel–Crafts acylation product with concomitant loss of the Cbz protecting group. The resulting piperidine derivative was then treated with benzyl chloroformate to give the tricyclic spiroketone **4** in excellent yield (93% from **10**).

Thus, starting from commercially available benzyl 4-oxo-1-piperidinecarboxylate (**5**), the novel tricyclic spiroketone **4** was successfully synthesized in nine steps and 40% overall yield. With a workable synthesis in hand, we turned our attention toward the development of a more efficient approach for the synthesis of **4**. Treatment of the conjugate addition product **7** with neat concentrated sulfuric acid at 90 °C overnight resulted in ester hydrolysis, decarboxylation, subsequent hydrolysis of the nitrile, and cyclization of the resulting acid in one pot, leading directly to the desired spirocyclic tetralone ring system with concomitant cleavage of Cbz protecting group. Treatment of the resulting crude product with benzyl chloroformate furnished the pure spirocyclic ketone **4** in 41% yield. This approach constituted a clear improvement over the previous route, since compound **4** was obtained in only four steps and 36% overall yield from commercially available **5**. However, from a practical standpoint, the use of a large quantity of concentrated sulfuric acid during the third reaction step was a potential limitation for large-scale synthesis. Indeed, the large amount of sodium sulfate produced during the neutralization step (using sodium hydroxide) rendered the workup very difficult.

We therefore investigated a third route for the synthesis of the spirocyclic ketone **4** (Scheme 2). Reaction of benzyl 4-oxo-1-piperidinecarboxylate (**5**) with Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) in pyridine in the presence of a catalytic amount of piperidine afforded alkylidenemalonate **11** in 82% yield. Treatment of **11** with benzylmagnesium chloride (2.5 equiv) in the presence of a catalytic amount of copper(I) iodide (0.036 equiv) gave the crude conjugate addition product, which was transformed to the key intermediate **10** in excellent yield (92% for two steps) simply by heating in a mixture of DMF/water (1:1). Under these reaction conditions the isopropylidene protecting group was cleaved leading to the diacid, which was simultaneously decarboxylated to provide the resulting carboxylic acid. Thus, the piperidine-4-acetic acid derivative **10** was prepared efficiently in three steps starting from benzyl 4-oxo-1-piperidinecarboxylate (**5**) with 75% overall yield. Carboxylic acid **10** was then converted to spirocyclic ketone **4** following the same reaction sequence as described above in good overall yield (93%).

Thus, starting from the commercially available *N*-Cbz protected piperidone **5**, the novel spirocyclic tetralone **4** was efficiently

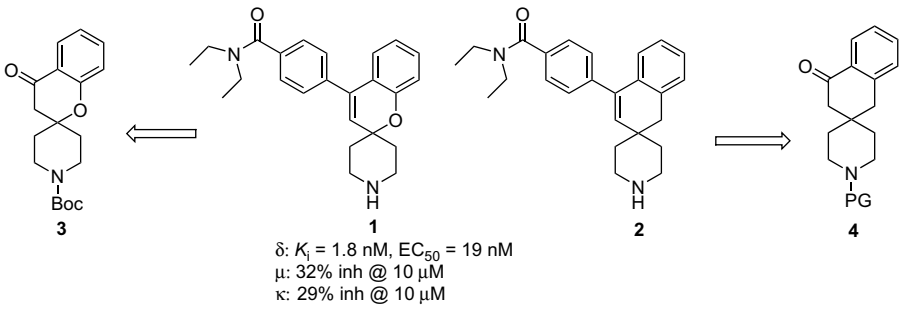
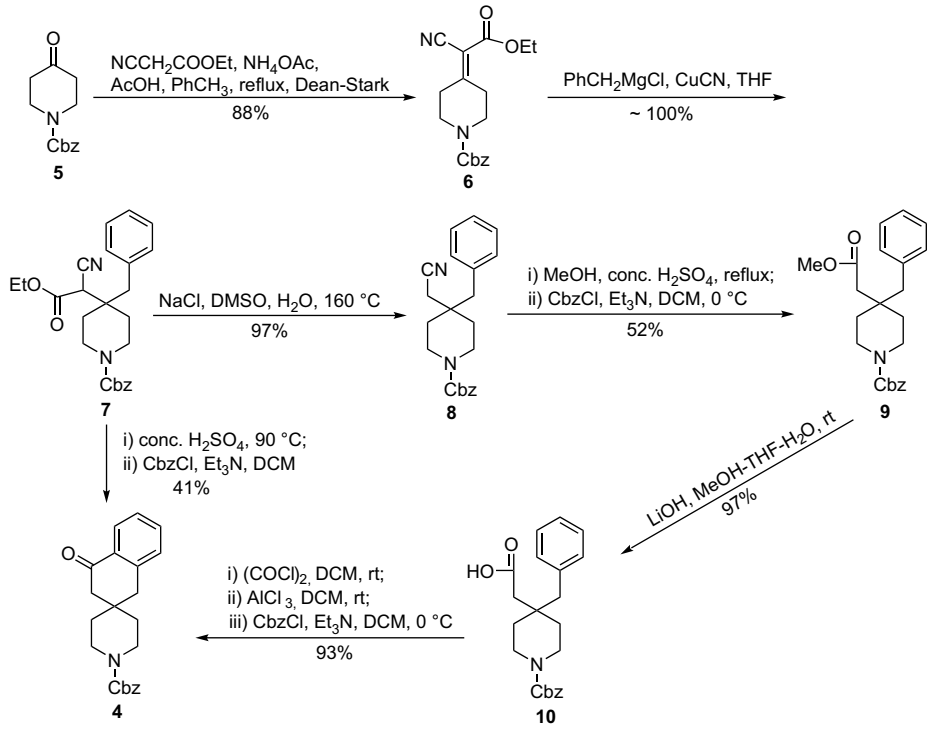


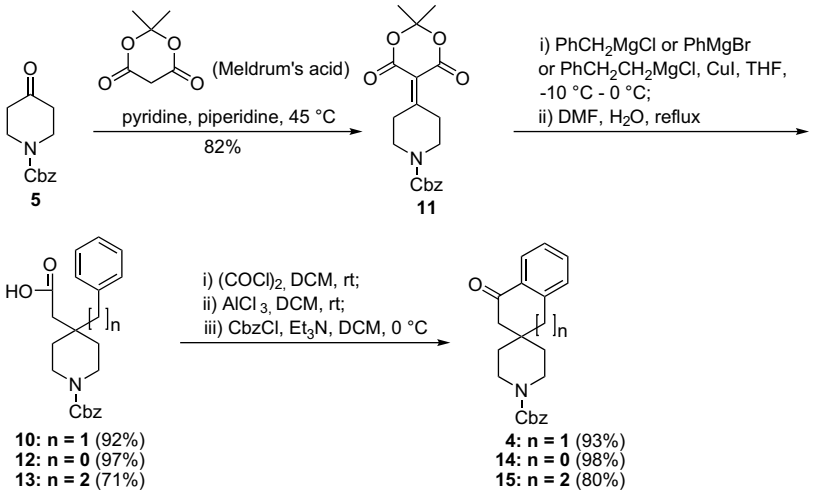
Figure 2. Tricyclic spiroketone scaffolds as key building blocks for the selective delta opioid receptor agonists.



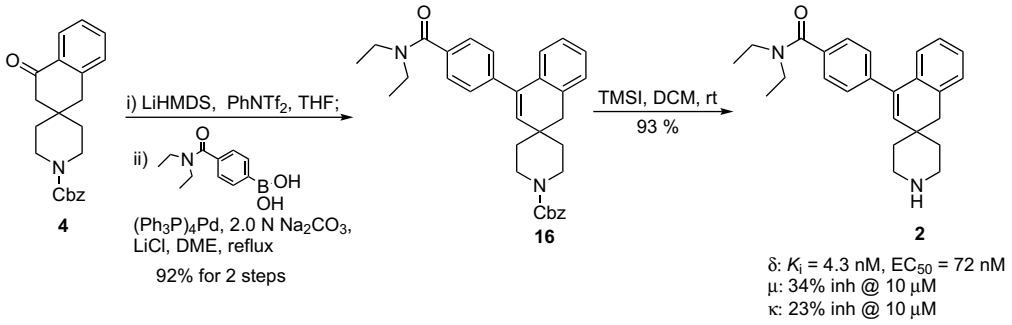
Scheme 1. The initial and second approaches to the tricyclic spiroketone **4**.

synthesized via six reaction steps with overall yield of 70%. This synthetic approach is suitable for large-scale synthesis, and also well-suited for the synthesis of other tricyclic spiroketone scaffolds of different ring size. For example, by following the same reaction sequence and using phenylmagnesium bromide or phenethylmagnesium choride in place of the benzylmagnesium chloride in the conjugate addition reaction (step 2), spirocyclic indanone **14**[12] and the novel spirocyclic benzocycloheptanone **15** were efficiently synthesized via the intermediate carboxylic acids **12** and **13**, respectively, in good overall yields (78%, 47% for **14**, **15**, respectively), as reported in Scheme 2.

Compound **2** was prepared in three steps and high overall yield from spirocyclic tetralone **4** (Scheme 3).[13] Hence, conversion of **4** to the corresponding enol triflate under standard condition followed by Suzuki–Miyaura cross-coupling with 4-(*N*,*N*-diethylaminocarbonyl)phenylboronic acid gave compound **16** in excellent yield (92%). Removal of the Cbz protective group of **16** by treatment with iodotrimethylsilane (TMSI) led to the target molecule **2** (93%). Compound **2** was tested for its affinities toward the cloned human delta, mu, and kappa opioid receptors as measured by its abilities to displace [^{3}H]-diprenorphine from its specific binding sites.[8] Replacement of the spiro[chromene-2,4′-piperidine] template of **1** with a 1*H*-spiro[naphthalene-2,4′-piperidine] scaffold was well tolerated. Indeed, compound **2** displayed high affinity and selectivity toward the delta opioid receptor (K_i=4.3 nM). In the guanosine 5′-*O*-(3-[^{35}S]thio)triphosphate ([^{35}S]GTPγS) functional assay, **2** was also identified as a potent agonist at the delta opioid receptor (EC_{50}=72 nM).



Scheme 2. General and efficient synthetic approach to tricyclic spiroketones.



Scheme 3. Synthesis of highly potent and selective delta opioid receptor agonist **2** from scaffold **4**.

3. Conclusion

We have developed three synthetic routes to the novel spirocyclic tetralone **4**. Our original approach consisted in a nine-step reaction sequence and 40% overall yield. The lengthy first-generation approach was significantly improved in our second route, which consisted of only four steps in similar overall yield. However, from the practical standpoint, the use of a large quantity of concentrated sulfuric acid during the synthesis was a potential limitation for large-scale synthesis. As a result, we investigated and successfully developed a third route. Starting from commercially available benzyl 4-oxo-1-piperidinecarboxylate (**5**), compound **4** was efficiently synthesized in a six-step sequence and excellent overall yield (70%). This synthetic approach is suitable for large-scale synthesis, and has been successfully applied to the synthesis of other tricyclic spiroketone scaffolds. Indeed, the spirocyclic indanone **14** and spirocyclic benzocycloheptanone **15** were efficiently synthesized in good overall yields (78%, 47% for **14**, **15**, respectively) by this approach. As an example of the utility of these novel scaffolds in drug discovery, spirocyclic tetralone **4** was used as the key building block for the synthesis of the novel delta opioid receptor agonist **2**. These novel building blocks could also have potential utilities for other medicinal chemistry programs.

4. Experimental procedures

4.1. General comments

All chemicals used were reagent grade and used as received. All the listed new compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, and HRMS, and the purity was higher than 95% as assessed by LC/MS. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Bruker 400 MHz spectrometer. They are reported in parts per million on the δ scale from TMS. LC/MS was performed on a Thermo-Finnigan Surveyor HPLC and a Thermo-Finnigan AQA MS using either positive or negative electrospray ionization. Program (positive): solvent A, 10 mM ammonium acetate, pH 4.5, 1% acetonitrile; solvent B, acetonitrile; column, Michrom Bioresources Magic C18 Macro Bullet; detector, PDA λ=220–300 nm; gradient, 96% A to 100% B in 3.2 min and hold 100% B for 0.4 min. Program (negative): solvent A, 1 mM ammonium acetate, pH 4.5, 1% acetonitrile; solvent B, acetonitrile; column, Michrom Bioresources Magic C18 Macro Bullet; detector, PDA λ=220–300 nm; gradient, 96% A to 100% B in 3.2 min and hold 100% B for 0.4 min. HRMS was performed by the Mass Spectrometry Service Laboratory at the Department of Chemistry, University of Minnesota. For flash column chromatography, silica gel (Merck, grade 9385, 230–400 mesh) was used. Melting points are uncorrected.

4.2. 4-(Cyano-ethoxycarbonyl-methylene)-piperidine-1-carboxylic acid benzyl ester (6)

To a solution of commercially available benzyl 4-oxo-1-piperidinecarboxylate (**5**) (37.26 g, 160 mmol) in toluene (450 mL) were added ethyl cyanoacetate (18.8 g, 166 mmol), acetic acid (2 mL), and ammonium acetate (1.24 g, 16 mmol). The reaction mixture was refluxed for 2 h with concomitant removal of water formed during the reaction using a Dean–Stark trap. Additional ethyl cyanoacetate (10 g, 88.4 mmol), acetic acid (2 mL), and ammonium acetate (1.24 g, 6 mmol) were added to the reaction mixture and then refluxed for another 1.5 h and additional amount of ethyl cyanoacetate (10 g, 88.4 mmol), acetic acid (2 mL), and ammonium acetate (1.24 g, 6 mmol) was added, and the resulting mixture was refluxed for another 1 h. The reaction mixture was cooled to room temperature and washed with saturated aqueous sodium bicarbonate (2×200 mL), and dried (Na_2SO_4). After evaporation of the solvent in vacuo, a mixture of hexane (300 mL) and ethyl acetate (20 mL) was added to the residue, and the mixture was kept at room temperature overnight. The solid was collected by filtration, washed with hexane, and dried in vacuo, yielding compound **6** (46 g, 88%) as a light-yellow solid: mp 90–91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 5H), 5.16 (s, 2H), 4.29 (q, J=7.0 Hz, 2H), 3.69 (t, J=6.0 Hz,, 2H), 3.62 (t, J=6.0 Hz, 2H), 3.15 (t, J=5.0 Hz, 2H), 2.79 (t, J=5.0 Hz, 2H), 1.35 (t, J=7.0 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 173.4, 161.4, 154.9, 136.3, 128.6, 128.2, 128.0, 114.9, 104.6, 67.6, 62.1, 43.7, 43.3, 35.2, 30.9, 14.0; HRMS m/z calcd for $C_{18}H_{20}N_2O_4Na$ $(M+Na)^+$ 351.1315, found 351.1304.

4.3. 4-Benzyl-4-(cyano-ethoxycarbonyl-methylene)-piperidine-1-carboxylic acid benzyl ester (7)

To a suspension of copper(I) cyanide (17.3 g, 193.2 mmol) in anhydrous tetrahydrofuran (400 mL) was added dropwise benzylmagnesium chloride (192 mL, 2.0 M in THF, 384 mmol) under nitrogen atmosphere at 0 °C. After the reaction mixture was stirred at room temperature for 2 h, a solution of compound **6** (31.5 g, 96 mmol) in tetrahydrofuran (100 mL) was added dropwise at −10 °C. After the addition, the reaction mixture was stirred at room temperature overnight, and then quenched with saturated aqueous ammonium chloride (500 mL) and filtered. The filtrate was extracted with ether (3×600 mL) and the combined organic extracts were dried (Na_2SO_4). Evaporation of the solvent provided the crude product, which was purified by flash chromatography on silica gel (hexane–ethyl acetate–methylene chloride, 4:1:1), to give compound **7** (40 g, ~100%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 8H), 7.18 (m, 2H), 5.11 (s, 2H), 4.25 (q, J=7.0 Hz, 2H), 3.74 (m, 2H), 3.63 (s, 1H), 3.54 (m, 2H), 3.05 (d, J=14.0 Hz, 1H), 2.93 (d, J=14.0 Hz, 1H), 1.91 (m, 1H), 1.69 (m, 3H), 1.31 (t, J=7.0 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 164.9, 155.2, 136.6, 135.2, 130.8,

128.6, 128.5, 128.3, 128.1, 127.9, 127.3, 115.4, 67.3, 62.8, 44.2, 39.9, 39.4, 39.3, 31.1, 29.7, 14.0; HRMS *m*/*z* calcd for $C_{25}H_{28}N_2O_4Na$ $(M+Na)^+$ 443.1941, found 443.1941.

4.4. 4-Benzyl-4-cyanomethyl-piperidine-1-carboxylic acid benzyl ester (8)

To a solution of compound **7** (6.0 g, 14.29 mmol) in dimethylsulfoxide (50 mL) were added sodium chloride (320 mg, 5.47 mmol) and water (0.6 mL). The reaction mixture was heated at 160 °C under nitrogen atmosphere for 2 h and then cooled to room temperature. Water (300 mL) was added to the mixture and then extracted with ether (2×300 mL). The organic layers were combined and dried (Na_2SO_4). Evaporation of the solvent provided the crude product, which was purified by flash chromatography on silica gel (hexane–ethyl acetate–methylene chloride, 4:1:1) to afford compound **8** (4.8 g, 97%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 4H), 7.34 (m, 1H), 7.32 (m, 2H), 7.27 (m, 1H), 7.18 (m, 2H), 5.13 (s, 2H), 3.70 (m, 2H), 3.42 (m, 2H), 2.80 (s, 2H), 2.23 (s, 2H), 1.62 (m, 2H), 1.54 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 155.2, 136.6, 135.7, 130.4, 128.5, 128.1, 127.9, 127.1, 117.7, 67.3, 43.0, 39.6, 35.5, 34.0, 25.1; HRMS *m*/*z* calcd for $C_{22}H_{24}N_2O_2Na$ $(M+Na)^+$ 371.1730, found 371.1725.

4.5. 4-Benzyl-piperidine-1,4-dicarboxylic acid 1-benzyl ester 4-methyl ester (9)

To a solution of compound **8** (3.0 g, 8.62 mmol) in methanol (80 mL) was added concentrated sulfuric acid (16 mL), and the mixture was heated at reflux under a nitrogen atmosphere for 2 days. The reaction mixture was cooled to 0 °C and basified by slow addition of 6 N aqueous sodium hydroxide to pH ~ 9 and then evaporated in vacuo to remove methanol. The mixture was extracted with methylene chloride (3×80 mL). Organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in methylene chloride (80 mL) and cooled to 0 °C. To this solution was added triethylamine (3.8 mL, 27.3 mmol) followed by dropwise addition of benzyl chloroformate (2.6 mL, 95%, 17.3 mmol). The reaction mixture was stirred at 0 °C for 1 h and washed with saturated aqueous $NaHCO_3$ (50 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane–ethyl acetate–methylene chloride, 4:1:1) to give compound **9** (1.70 g, 52%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 5H), 7.27 (m, 3H), 7.20 (m, 2H), 5.12 (s, 2H), 3.74 (m, 2H), 3.70 (s, 3H), 3.34 (m, 2H), 2.81 (s, 2H), 2.29 (s, 2H), 1.52 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 172.2, 155.4, 137.1, 136.9, 130.9, 128.5, 128.1, 128.0, 127.8, 126.4, 67.1, 51.4, 43.4, 39.8, 38.8, 35.5, 34.4; HRMS *m*/*z* calcd for $C_{23}H_{27}NO_4Na$ $(M+Na)^+$ 404.1832, found 404.1844.

4.6. Benzyl 4-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)piperidine-1-carboxylate (11)

To a mixture of benzyl 4-oxo-1-piperidinecarboxylate (**5**) (29.8 g, 127.7 mmol) and Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) (18.4 g, 127.7 mmol) was added pyridine (12.5 mL) followed by 10 drops of piperidine. The mixture was stirred at 45 °C under nitrogen atmosphere for 1 h and then kept at room temperature overnight. To the resulting solid was added methanol, and the solid was collected by filtration, washed with methanol, dried in vacuo to yield compound **11** (37.65 g, 82%) as a white solid: mp 147–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 5H), 5.17 (s, 2H), 3.69 (br s, 4H), 3.18 (br s, 4H), 1.74 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 176.4, 160.6, 155.0, 136.4, 128.6, 128.2, 128.0, 115.7, 104.0, 67.5, 43.3, 33.1, 27.2; HRMS *m*/*z* calcd for $C_{19}H_{21}NO_6Na$ $(M+Na)^+$ 382.1261, found 382.1251.

4.7. 4-Benzyl-piperidine-1,4-dicarboxylic acid monobenzyl ester (10)

4.7.1. Method A from ester 9

Compound **9** (1.6 g, 4.2 mmol) was dissolved in methanol–tetrahydrofuran–water (40 mL/40 mL/40 mL), and the resulting solution was treated with lithium hydroxide (1.26 g, 30 mmol). The reaction mixture was stirred at room temperature overnight, concentrated in vacuo, acidified with 3 N HCl, and extracted with methylene chloride (3×50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to yield compound **10** (1.5 g, 97%) as an off-white solid: mp 137–138 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.25 (br s, 1H), 7.33 (m, 7H), 7.21 (m, 3H), 5.06 (s, 2H), 3.61 (br s, 2H), 3.33 (br s, 2H), 2.78 (s, 2H), 2.18 (s, 2H), 1.46 (m, 2H), 1.39 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 177.3, 155.4, 136.9, 136.8, 130.9, 128.5, 128.1, 128.0, 127.9, 126.5, 67.2, 43.3, 39.8, 38.7, 35.5, 34.4; HRMS *m*/*z* calcd for $C_{22}H_{25}NO_4Na$ $(M+Na)^+$ 390.1676, found 390.1673.

4.7.2. Method B from compound 11

To a suspension of CuI (550 mg, 2.88 mmol) in anhydrous tetrahydrofuran (600 mL) was added dropwise a 2.0 M solution of benzylmagnesium chloride (100 mL, 200 mmol) in tetrahydrofuran under nitrogen atmosphere at −10 °C. After the reaction mixture was stirred at −10 °C for 30 min, compound **11** (28.72 g, 80 mmol) was added in 10 portions over 1 h period. After the addition, the reaction mixture was stirred between −10 °C and −0 °C for 3 h, and then quenched with a mixture of concd NH_4OH–satd NH_4Cl–H_2O (1:2:3, 400 mL). The mixture was extracted with ethyl acetate, and the combined organic layers were washed with a mixture of concd NH_4OH–satd NH_4Cl–H_2O (1:2:3, 3×200 mL) and brine (3×200 mL), dried (Na_2SO_4), and concentrated in vacuo. To the residue was added diethyl ether and the mixture was stirred overnight at room temperature. The product was collected by filtration, washed with diethyl ether, and dried in vacuo, yielding the crude conjugate addition product as a yellow powder (37.8 g), which was used directly for the next step. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32–7.25 (m, 5H), 7.15 (t, *J*=7.2 Hz, 2H), 7.07 (t, *J*=7.2 Hz, 1H), 7.00 (d, *J*=7.2 Hz, 2H), 4.95 (s, 2H), 3.67 (m, 2H), 2.95 (m, 2H), 2.76–2.72 (m, 2H), 2.73 (s, 2H), 1.44 (s, 6H), 0.80 (m, 2H).

The above crude product was dissolved in a mixture of DMF (200 mL) and water (200 mL), and the resulting solution heated at 135 °C under nitrogen atmosphere for 2 days, then cooled to room temperature. To the reaction mixture were added 1 N sodium hydroxide (125 mL) and water (500 mL), the resulting mixture was extracted with diethyl ether, and the aqueous layer was separated, acidified with 6 N aqueous hydrochloric acid, and extracted with diethyl ether. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane–acetone, 1:2) to furnish carboxylic acid **10** (26.9 g, 92% for two steps) as an off-white solid.

4.8. 2-(1-(Benzyloxycarbonyl)-4-phenylpiperidin-4-yl)acetic acid (12) and 2-(1-(benzyloxycarbonyl)-4-phenethylpiperidin-4-yl)acetic acid (13)

Acids **12** and **13** were prepared in the same manner as method B for acid **10** as described above except that phenylmagnesium bromide and phenethylmagnesium chloride replaced the benzylmagnesium chloride in the conjugate addition reaction, respectively.

Starting from compound **11** (21.54 g, 60 mmol), acid **12** (20.5 g, 97%) was isolated as an off-white solid: mp 137–138 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.79 (br s, 1H), 7.34 (m, 9H), 7.19 (t, *J*=7.0 Hz, 1H), 5.06 (s, 2H), 3.58 (br s, 2H), 3.20 (br s, 2H), 2.57 (s, 2H), 2.11 (m, 2H), 1.94 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 155.4, 142.6, 136.8, 128.7, 128.5, 128.3, 128.0, 127.8, 126.7, 126.6, 67.1, 40.4, 39.2, 34.9; HRMS *m*/*z* calcd for $C_{21}H_{23}NO_4Na$ $(M+Na)^+$ 376.1519, found 376.1509.

Starting from compound **11** (21.54 g, 60 mmol), acid **13** (16.2 g, 71%) was isolated as an off-white solid: mp 84–85 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.17 (br s, 1H), 7.35 (m, 5H), 7.26 (t, J=7.0 Hz, 2H), 7.17 (m, 3H), 5.07 (s, 2H), 3.48 (br s, 2H), 3.34 (m, 2H), 2.53 (m, 2H), 2.37 (s, 2H), 1.65 (m, 2H), 1.57 (m, 2H), 1.45 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 176.8, 155.5, 142.2, 136.8, 128.5, 128.5, 128.3, 128.0, 127.9, 125.9, 67.2, 40.4, 39.7, 39.4, 34.8, 34.6, 29.6; HRMS m/z calcd for $C_{23}H_{27}NO_4Na$ $(M+Na)^+$ 404.1832, found 404.1820.

4.9. Benzyl 4-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,4′-piperidine]-1′-carboxylate (4)

4.9.1. Method A from acid *10*

To a solution of acid **10** (27 g, 73.6 mmol) in anhydrous methylene chloride (200 mL) was added oxalyl chloride (39 mL, 447 mmol) in one portion followed by a few drops of anhydrous dimethylformamide. The reaction mixture was stirred at room temperature for 4 h and then concentrated in vacuo. The resulting acyl chloride was dissolved in anhydrous methylene chloride (800 mL) and aluminum chloride (20 g, 150 mmol) was added in one portion under nitrogen atmosphere at room temperature. The reaction mixture was stirred at room temperature overnight and then cooled to 0 °C, quenched by water (400 mL) followed by addition of concentrated ammonium hydroxide to make the aqueous layer basic. The organic layer was separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was then dissolved in methylene chloride (600 mL) and cooled to 0 °C. To this solution was added triethylamine (30 mL, 215.6 mmol) followed by dropwise addition of benzyl chloroformate (22.5 mL, 149.7 mmol). The reaction mixture was stirred at 0 °C for 1 h and then washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography (hexane–ethyl acetate–methylene chloride, 4:1:1) to yield the tricyclic spirotetralone **4** (23.88 g, 93%) as a pale-yellow solid: mp 110–111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, J=7.0, 1.0 Hz, 1H), 7.51 (dt, J=8.0, 1.0 Hz, 1H), 7.35–7.30 (m, 6H), 7.25 (d, J=8.0 Hz, 1H), 5.13 (s, 2H), 3.52 (m, 4H), 2.98 (s, 2H), 2.62 (s, 2H), 1.50 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 197.1, 155.3, 141.0, 136.8, 134.0, 132.0, 129.4, 128.5, 128.0, 127.8, 127.0, 126.8, 67.1, 49.0, 40.4, 39.6, 35.2, 35.0; HRMS m/z calcd for $C_{22}H_{23}NO_3Na$ $(M+Na)^+$ 372.1570, found 372.1572.

4.9.2. Method B from cyanoacetate **7**

Concentrated sulfuric acid (210 mL) was added slowly to compound **7** (38 g, 90.5 mmol) at 0 °C under nitrogen atmosphere. The mixture was warmed to room temperature, stirred for 30 min at room temperature, and then heated at 90 °C overnight. The reaction mixture was cooled with ice-bath and carefully basified with 6 N aqueous sodium hydroxide to pH=9–10. The mixture was extracted with methylene chloride (3×800 mL), and the organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in methylene chloride (500 mL) and treated with benzyl chloroformate (16 mL, 106.5 mmol) and triethylamine (30 mL, 215.6 mmol) followed by purification on silica gel as described above, furnishing spiroketone **4** (13 g, 41%), which was identical with the product prepared by method A.

4.10. Benzyl 3-oxo-2,3-dihydrospiro[indene-1,4′-piperidine]-1′-carboxylate (14) and benzyl 5-oxo-5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,4′-piperidine]-1′-carboxylate (15)

Spirocyclic ketones **14** and **15** were prepared from acids **12** and **13**, respectively, by using the same reaction conditions of method A for compound **4** as described above.

Starting from acid **12** (2.48 g, 7.03 mmol), spirocyclic indanone **14** (2.3 g, 98%) was isolated as an off-white solid: mp 155–156 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J=8.0 Hz, 1H), 7.65 (dt, J=8.0, 1.0 Hz, 1H), 7.47 (d, J=8.0 Hz, 1H), 7.43 (d, J=8.0 Hz, 1H), 7.39 (m, 4H), 7.35 (m, 1H), 5.18 (s, 2H), 4.33 (br s, 2H), 2.94 (br s, 2H), 2.65 (s, 2H), 1.98 (m, 2H), 1.53 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 204.3, 161.8, 155.3, 136.7, 135.7, 135.2, 128.5, 128.2, 128.1, 128.0, 123.9, 123.8, 67.3, 47.0, 42.0, 41.5, 37.6; HRMS m/z calcd for $C_{21}H_{21}NO_3Na$ $(M+Na)^+$ 358.1414, found 358.1410.

Starting from acid **13** (16.0 g, 42.0 mmol), spirocyclic benzocycloheptanone **15** (12.2 g, 80%) was isolated as an off-white solid: mp 76–78 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, J=8.0, 1.0 Hz, 1H), 7.40 (dd, J=8.0, 1.0 Hz, 1H), 7.37 (m, 4H), 7.33 (m, 1H), 7.29 (m, 1H), 7.24 (m, 1H), 5.14 (s, 2H), 3.54 (m, 4H), 3.04 (br s, 2H), 2.75 (s, 2H), 1.78 (m, 2H), 1.64 (br s, 2H), 1.50 (br s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 201.4, 155.4, 144.7, 138.3, 136.9, 131.8, 130.2, 128.7, 128.5, 128.0, 127.9, 126.4, 67.1, 50.7, 40.0, 38.5, 36.2, 34.2, 30.5; HRMS m/z calcd for $C_{23}H_{25}NO_3Na$ $(M+Na)^+$ 386.1727, found 386.1725.

4.11. Benzyl 4-(4-(diethylcarbamoyl)phenyl)-1*H*-spiro[naphthalene-2,4′-piperidine]-1′-carboxylate (16)

A 1.0 M solution of lithium bis(trimethylsilyl)amide (3.6 mL, 3.6 mmol) was added at −78 °C under nitrogen atmosphere to a solution of compound **4** (1.047 g, 3.0 mmol) in anhydrous tetrahydrofuran (30 mL). After 45 min, a solution of *N*-phenyltrifluoromethanesulfonimide (1.3 g, 3.6 mmol) in tetrahydrofuran (8 mL) was added dropwise. The reaction mixture was then warmed to room temperature and stirred for 2.5 h, quenched by addition of water (40 mL), and extracted with a mixture of hexane and ether (1:1, 3×50 mL). The organic extracts were combined and washed with water (2×60 mL), brine (60 mL) and dried (Na_2SO_4). Evaporation of the solvent gave the crude enol triflate as a yellow oil, which was used directly for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.18 (m, 9H), 5.98 (s, 1H), 5.11 (s, 2H), 3.70 (m, 2H), 3.40 (m, 2H), 2.83 (s, 2H), 1.66–1.56 (m, 4H).

To the solution of above crude enol triflate in 1,2-dimethoxyethane (25 mL) were added 2.0 M aqueous sodium carbonate (5 mL, 10 mmol), lithium chloride (424 mg, 10 mmol), 4-(*N*,*N*-diethylaminocarbonyl)phenylboronic acid (796 mg, 3.6 mmol), and tetrakis(triphenylphosphine)palladium(0) (104 mg, 0.09 mmol). The reaction mixture was refluxed under nitrogen atmosphere overnight, cooled to room temperature, diluted with water (30 mL), and extracted with ether (3×50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane–ethyl acetate–methylene chloride, 2:1:1) to furnish the coupling product **16** as an off-white foam (1.4 g, 92% for two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.32 (m, 9H), 7.19 (m, 2H), 7.13 (m, 1H), 6.99 (d, J=8.0 Hz, 1H), 6.00 (s, 1H), 5.14 (s, 2H), 3.70 (br s, 2H), 3.57 (br s, 2H), 3.46 (m, 2H), 3.33 (br s, 2H), 2.82 (s, 2H), 1.64 (br s, 2H), 1.53 (br s, 2H), 1.26 (br s, 3H), 1.16 (br s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.1, 155.4, 141.3, 139.0, 136.9, 136.4, 134.9, 134.4, 133.9, 128.8, 128.5, 128.0, 127.9, 127.7, 126.6, 126.5, 125.7, 67.0, 43.4, 40.6, 40.2, 39.3, 34.8, 33.4, 14.4, 13.0; HRMS m/z calcd for $C_{33}H_{36}N_2O_3Na$ $(M+Na)^+$ 531.2618, found 531.2626.

4.12. *N*,*N*-Diethyl-4-(1*H*-spiro[naphthalene-2,4′-piperidine]-4-yl)benzamide (2)

Iodotrimethylsilane (0.29 mL, 2 mmol) was added to the solution of compound **16** (508 mg, 1.0 mmol) in anhydrous methylene chloride (10 mL) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 2 h and quenched with 1 N hydrochloric acid (30 mL), extracted with ether (2×60 mL). The aqueous was basified with 3 N aqueous sodium hydroxide to pH=9–10, and extracted with methylene chloride (3×40 mL). The

organic extracts were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in methylene chloride (3 mL) and diluted with ether (15 mL). To this solution was added hydrogen chloride (1.5 mL, 2.0 M in ether, 3 mmol) and stirred at room temperature for 30 min. The precipitated solid was collected by filtration and washed with ether, dried in vacuo to give the target molecule **2** (380 mg, 93%) as HCl salt and an off-white solid: mp 275 °C dec. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (br s, 1H), 8.93 (br s, 1H), 7.44 (d, J=8.0 Hz, 2H), 7.39 (d, J=8.0 Hz, 2H), 7.32 (dd, J=8.0, 1.0 Hz, 1H), 7.24 (dt, J=8.0, 1.0 Hz, 1H), 7.18 (dt, J=8.0, 1.0 Hz, 1H), 6.94 (dd, J=8.0, 1.0 Hz, 1H), 6.18 (s, 1H), 3.45 (br s, 2H), 3.21 (m, 6H), 2.83 (s, 2H), 1.69 (m, 4H), 1.12 (m, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.0, 140.6, 140.2, 136.6, 133.9, 133.3, 131.8, 128.8, 128.6, 128.2, 126.9, 126.4, 126.0, 43.4, 40.3, 39.3, 32.3, 31.5, 14.3, 12.9; HRMS m/z calcd for $C_{25}H_{31}N_2O$ $(M+H)^+$ 375.2431, found 375.2431.

Supplementary data

Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **2**, **4**, **6**–**16**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.04.094.

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