Efficient Synthesis of 5-Alkoxy-(3*R*)-hydroxy-2,3-dihydrospiro[indene-1,4′-piperidines]: A Novel Scaffold for Renin Inhibitors

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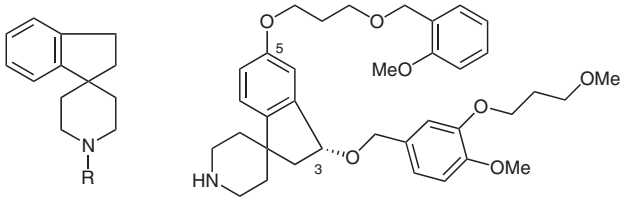
Abstract: We report herein, an efficient synthetic method for the preparation of a 5-alkoxy-(3*R*)-hydroxy-2,3-dihydrospiro[indene-1,4′-piperidines] scaffold using a regioselective intermolecular reaction and a stereoselective reduction as key steps. Compound **2**, based on this scaffold, showed moderate *in vitro* binding affinity for purified human renin.

Key words: CBS reduction, regioselectivity, spiro-piperidine, stereoselectivity, renin

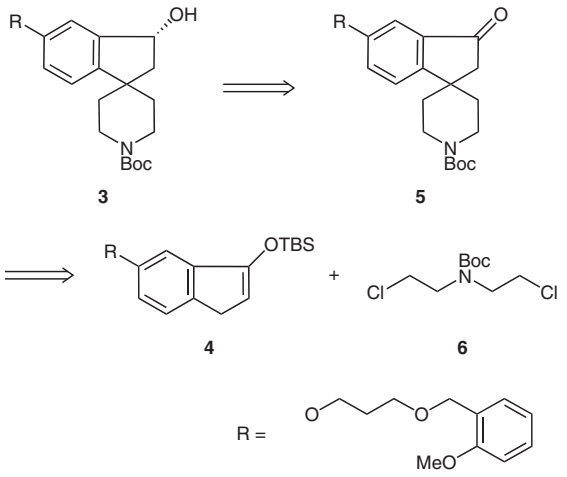
Structural motifs that are commonly found in several series of inhibitors or ligands against different drug targets, are known as privileged structures.[1] 2,3-Dihydrospiro[indene-1,4′-piperidine] (**1**) is one of these privileged structures for the broad class of seven-transmembrane G-protein coupled receptor ligands (Figure 1).[2] In recent years, small molecule renin inhibitors having novel 4-phenylpiperidine moieties as the central scaffold have been reported.[3] Based on this information, we designed and prepared several 2,3-dihydrospiro[indene-1,4′-piperidine]-based compounds as replacements for the piperidine. As a result, the 3,5-disubstituted derivative of **1**, compound **2**, displayed moderate binding affinity (IC_{50} = 33 nM) to human renin.[4] This result indicated that derivatives having suitable substituents at the 3- and 5-positions of **1** could become new molecule leads for renin inhibitors.



1 **2**: IC_{50} = 33 nM

Figure 1

In this paper, we report an efficient synthetic method for the preparation of 3,5-disubstituted (*R*)-**3** derivatives using easily available indanones as starting materials. Regarding the synthesis of the central spiro-piperidine unit, a few synthetic approaches have been reported.[5] These routes utilize Friedel–Crafts acylation toward (4-phenylpiperidin-4-yl)acetic acid analogues, and intermolecular cyclizaion of indene with dialkyl halides. However, some problems remain, such as the generation of regioisomers and the multi-step nature of the reactions. The key features of our strategy are regioselective construction of a spiro-piperidine ring at the 1-position of silyl enol ether **4**, and stereoselective reduction at the 3-position of ketone **5** (Scheme 1). We planned to utilize **4** and *N*-Boc dichloride **6** for the preparation of **5**, and a Corey–Bakshi–Shibata (CBS) reduction[6] for the preparation of (*R*)-**3**.



Scheme 1

The preparation of **5** is described in Scheme 2. Commercially available 6-hydroxy-1-indanone (**7**) was alkylated with 1-[(3-bromopropoxy)methyl]-2-methoxybenzene (**8**) in the presence of potassium carbonate and treated with a catalytic amount of potassium iodide to afford 6-alkoxy-1-indanone **9** in 90% yield. The reaction of **9** with *tert*-butyldimethylsilyl chloride (TBSCl) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave **4** in 98% yield. The first key reaction, regioselective construction of the spiro-piperidine ring, was achieved by the following procedure. Deprotonation of **4** with lithium hexamethyldisilazide (LHMDS) at –78 °C and the subsequent reaction of the lithium salt with **6** at 0 °C, afforded spiro-piperidine **10** in 65% yield. In this reaction, no other regioisomers were observed. Other bases, such as potassium hexamethyldisilazide (KHMDS) and lithium diisopropylamide (LDA),

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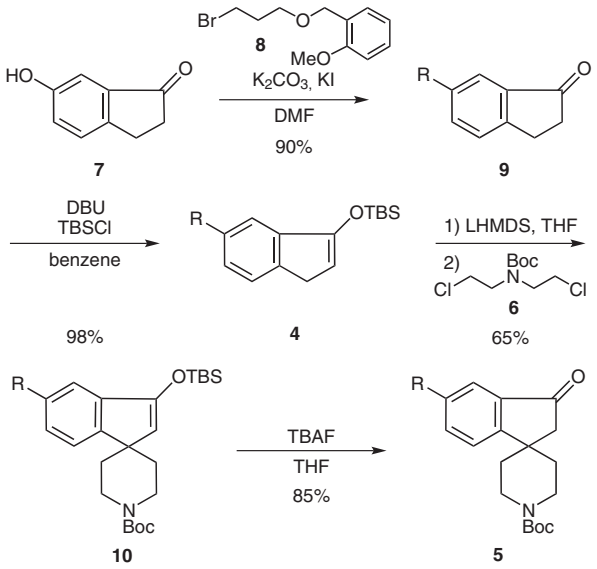
resulted in poor yields. Spiro-piperidine **10** was easily converted into **5** by treatment with tetrabutylammonium fluoride (TBAF) in 85% yield. Alternatively, conversion of **10** into **5** was accomplished by adding aqueous hydrogen chloride to the reaction mixture.

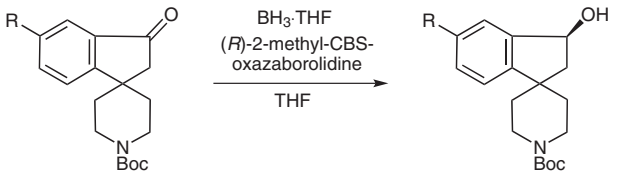


Scheme 2

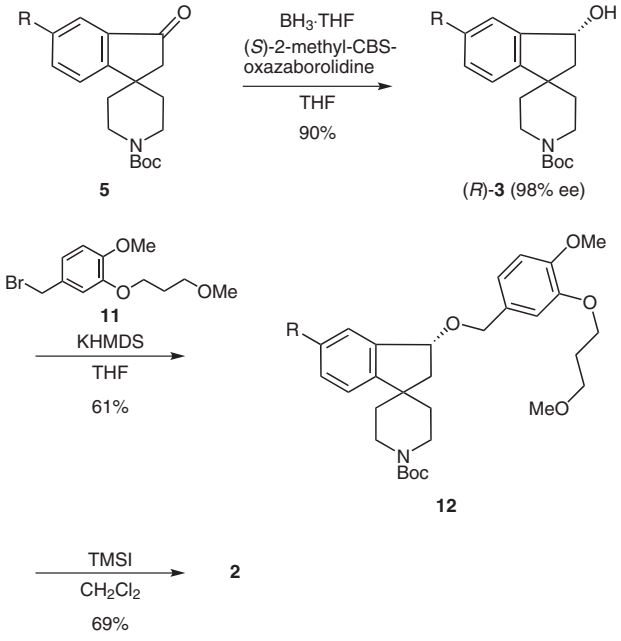
Next, we focused our efforts on the second key reaction, the CBS reduction of **5**. Asymmetric reduction to afford alcohol (*S*)-**3** using (*R*)-2-methyl-CBS-oxazaborolidine as a catalyst, was investigated under various conditions (temperature, solvent, and amount of catalyst and reducing agent), and the results are summarized in Table 1. Initially, we obtained (*S*)-**3** with 70% ee[7] in 86% yield (entry 1). Using 0.1 equivalent of catalyst led to improved results (89% ee, entry 2), but lowering the reaction temperature (–30 °C) decreased the enantioselectivity (83% ee, entry 3). To our delight, the highest ee was achieved when the reduction was carried out at 20 °C (94% ee, entry 4). We assumed that the coordination of the catalyst–BH_3 complex with **5** would be the determining step for the enantioselectivity. Because the coordination would be slower at low temperature, the non-catalyzed reduction of **5** with BH_3–THF would lead to a drop in the ee value. Other asymmetric reductions using (+)-*B*-chlorodiisopinocampheylborane[8] did not proceed.

Under conditions similar to those given in entry 4, ketone **5** was reduced with (*S*)-2-methyl-CBS-oxazaborolidine to afford (*R*)-**3** with 98% ee in 90% yield (Scheme 3). Deprotonation of **3** with KHMDS, followed by alkylation of the resulting alkoxide with 4-(bromomethyl)-1-methoxy-2-(3-methoxypropoxy)benzene (**11**), afforded benzyl ether **12** in 61% yield. In the final step, the removal of the Boc group with trimethylsilyl iodide (TMSI) gave the desired compound **2** in 69% yield. This synthetic strategy was also proven to be effective in the preparation of other 5-substituted spiro[(2-indanone)-1,4′-piperidines] (**14a** and **14b**) that possess electron-withdrawing or electron-donating substituents (Scheme 4). We believe that this synthetic method will also be applicable to the preparation of 6-substituted 3-hydroxy-2,3-dihydrospiro[indene-1,4′-piperidines] by using the corresponding 5-substituted 1-indanones as starting materials.

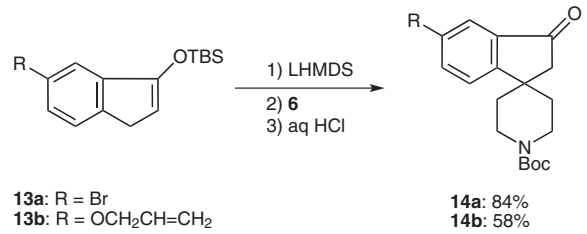
Table 1 CBS Reduction of **5** Catalyzed by (*R*)-2-Methyl-CBS-oxazaborolidine with BH_3–THF



Entry	BH_3 (equiv)	Catalyst (equiv)	Temp (°C)	Yield (%)	ee (%) of (*S*)-**3**
1	0.6	0.05	–10	86	70
2	0.6	0.1	–10	92	89
3	0.6	0.1	–30	88	83
4	0.6	0.1	20	86	94



Scheme 3



Scheme 4

In conclusion, we have achieved the development of an efficient synthetic method for the preparation of (*R*)-**3**.[9] In this method, its regio- and stereoselectivity were almost completely controlled and the total yield was satisfactory, whereas the yield of the spiro annulation reaction (**4** to **9**) was moderate. With a practical synthetic route to (*R*)-**3** in hand, further chemical modifications aimed at exploring novel renin inhibitors using (*R*)-**3** as a key intermediate are under way. The results of this work will be published elsewhere.

Acknowledgment

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(4) Compound **2** was evaluated as a 0.5 fumaric acid salt. The absolute stereochemistry of **2** was determined by an X-ray crystal structure complex with renin (data not shown).

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(7) The ee of **3** was determined by HPLC analysis (CHIRALCEL OJ-H; 4.6 × 250 mm; *n*-hexane–EtOH, 80:20; 0.5 mL/min), t_R of (*S*)-isomer = 24.6 min; t_R of (*R*)-isomer = 23.0 min.

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(9) **Synthesis of spiro-piperidine 5**: To a solution of silyl enol ether **4** (1.0 g, 2.30 mmol) in anhydrous THF (4.5 mL), was added LHMDS (1.0 M in THF, 5.8 mL, 5.8 mmol) at –78 °C. The mixture was stirred at the same temperature for 30 min, then a solution of *N*-Boc dichloride **6** (0.67 g, 2.79 mmol) in anhydrous THF (2.3 mL) was added. The mixture was warmed to 0 °C and stirred at the same temperature. After 8 h, 1N HCl (9.2 mL, 9.2 mmol) was added and the resulting mixture was stirred for a further 1 h. After extraction of the reaction mixture with EtOAc, the organic extract was washed with H_2O, sat. aq $NaHCO_3$, and brine then dried over anhydrous Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by silica gel flash column chromatography (*n*-hexane–EtOAc, 2:1) to afford spiro-piperidine **5** (0.58 g, 51% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.33 (m, 2 H), 7.26–7.23 (m, 1 H), 7.20 (dd, *J* = 8.3, 2.4 Hz, 1 H), 7.16 (d, *J* = 2.4 Hz, 1 H), 6.92 (t, *J* = 7.6 Hz, 1 H), 6.85 (d, *J* = 8.3 Hz, 1 H), 4.56 (s, 2 H), 4.22 (br s, 2 H), 4.15–4.10 (m, 2 H), 3.81 (s, 3 H), 3.69 (t, *J* = 6.1 Hz, 2 H), 2.84 (br s, 2 H), 2.63 (s, 2 H), 2.13–2.08 (m, 2 H), 1.98–1.92 (m, 2 H), 1.50 (s, 9 H), 1.46 (br s, 2 H). MS-FAB: *m*/*z* = 496 $[M + H]^+$.
Synthesis of (*R*)-3: To a solution of (*S*)-2-methyl-CBS-oxazaborolidine (1.0 M in toluene, 43 μL, 0.043 mmol) in anhydrous THF (0.2 mL), a solution of spiro-piperidine **5** (215 mg, 0.43 mmol) in anhydrous THF (0.2 mL) and BH_3·THF complex (1.0 M in THF, 0.26 mL, 0.26 mmol) were added. The resulting mixture was stirred at r.t. for 30 min, followed by the addition of MeOH and H_2O under ice-cooling. After extraction of the reaction mixture with EtOAc, the organic extract was washed with brine and dried over anhydrous Na_2SO_4. The solvent was then removed in vacuo, and the residue was purified by silica gel flash column chromatography (*n*-hexane–EtOAc, 1:1) to afford (*R*)-**3** (194 mg, 90% yield) as a colorless oil of optical purity 98% ee. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.35 (m, 1 H), 7.27–7.23 (m, 1 H), 7.08 (d, *J* = 8.3 Hz, 1 H), 6.96–6.91 (m, 2 H), 6.89–6.83 (m, 2 H), 5.22 (dd, *J* = 12.2, 6.8 Hz, 1 H), 4.56 (s, 2 H), 4.15–4.03 (m, 4 H), 3.81 (s, 3 H), 3.70 (t, *J* = 6.1 Hz, 2 H), 2.98–2.88 (m, 2 H), 2.53 (dd, *J* = 13.4, 7.1 Hz, 1 H), 2.12–2.07 (m, 2 H), 1.93–1.87 (m, 2 H), 1.73 (d, *J* = 6.8 Hz, 1 H), 1.69 (dd, *J* = 12.5, 4.2 Hz, 1 H), 1.60 (dd, *J* = 13.2, 2.0 Hz, 1 H), 1.47 (s, 9 H), 1.37 (br d, *J* = 13.2 Hz, 1 H). MS-FAB: *m*/*z* = 497 $[M]^+$.