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Synthesis of the *kappa-agonist* CJ-15,161 *via* a palladium-catalyzed cross-coupling reaction

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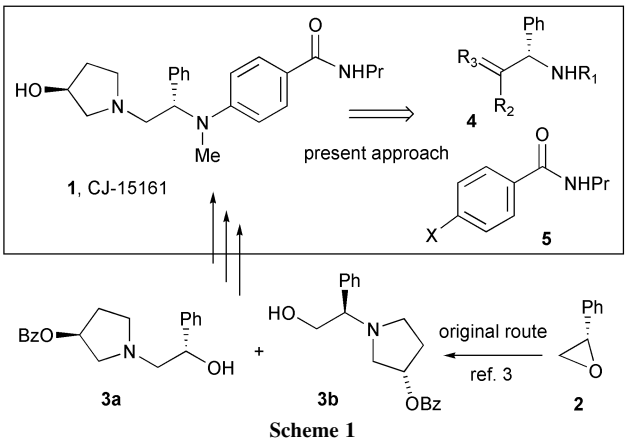
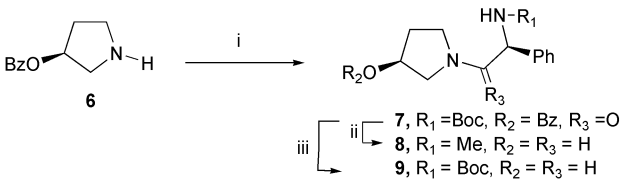
Syntheses of CJ-15,161 (1) involving intermolecular N-arylation of an appropriately functionalized diamine, obtained from the precursor α-amino acids or, more conveniently, from the corresponding 1,2-amino alcohols *via* 1,2,3-oxathiazolidine-2,2-dioxide 22, are reported.

During the past few years, significant progress has been made in the development of Pd-catalyzed cross-coupling of amines and aryl halides.[1] The ability to utilize relatively inexpensive aryl chlorides[2] has further enhanced the scope of the process, particularly in an industrial sense. We became interested in this area in the course of developing a fundamentally different synthetic strategy to a potential *kappa* receptor agonist, CJ-15,161 (**1**), that would be convergent as well as amenable to scale-up. The major limitations to the original synthetic route (Scheme 1)[3] involving chiral oxirane **2**, besides low overall yield and the noncrystalline nature of the intermediates, included poor regioselectivity during epoxide ring opening resulting in an inseparable mixture of regioisomers **3a**,**b**. We envisioned that a straightforward approach to these systems would involve a transition metal-mediated amination as the key step in the synthetic sequence using derivatives of phenylglycine **4** as the chiral amine source. We report here a facile synthesis of **1**, which explores an alternative disconnection relying on formation of the aniline residue by a palladium-mediated C–N bond forming step.

Model studies with *N*-methyl benzyl amine and 4-fluorobenzamide showed an extremely sluggish S_NAr even at elevated temperature, while the corresponding aryl bromides showed promising results when palladium-mediated coupling conditions were used. Encouraged by these results, efforts were then directed to apply the sequence on our substrate. The desired secondary amide **7** was prepared from 3-pyrrolidinol benzoate (**6**) and Boc-phenylglycine following standard peptide coupling conditions in high yield with no detectable epimerization. Simultaneous reduction of the amide carbonyl, reductive removal of the benzoate, and reduction of the N-Boc of **7** to the N–Me derivative **8** was efficiently done in one pot in the presence of excess $LiAlH_4$ at 80 °C. A controlled reduction



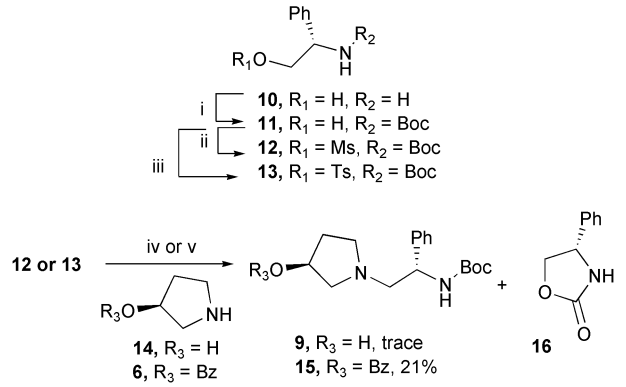
Scheme 1



Scheme 2 *Reagents and conditions*: (i) BocPhGly, DCC, HOBt, CH_2Cl_2, 90%; (ii) LAH (5 equiv.), toluene, 0 to 80 °C, 18 h, 70%; (iii) LAH (2.5 equiv.), toluene, 0 °C, 1 h, 80%.

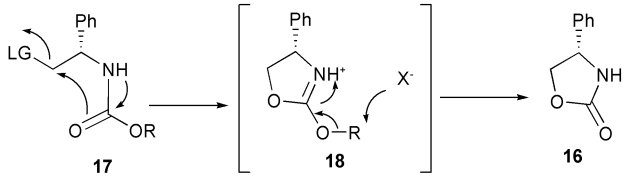
(Scheme 2) followed by quench at 0 °C was conveniently used to isolate Boc protected amine **9**, cleanly.

Alternatively, to avoid scale-up-related issues including epimerization of amide **7**, we decided to use Boc-protected mesylate **12** or tosylate **13**[4] derived from 1,2-aminol **10** as the chiral source (Scheme 3). However, attempts to displace either **12** or **13** with pyrrolidinols **14** or **6** produced oxazolidinone **16** as a major byproduct**,** presumably by intramolecular displacement of the intermediate sulfonate with the carbamate carbonyl (Scheme 4).[5]



Scheme 3 *Reagents and conditions*: (i) Boc_2O, THF, 91%; (ii) MsCl, Et_3N, CH_2Cl_2, 84%; (iii) TsCl, Et_3N, CH_2Cl_2, 90%; (iv) **12** or **13**, **14**, THF/DMF, 45–55 °C, trace; (v) **12**, **6**, THF/DMF, 40–5 °C, 21%.

In order to minimize byproduct formation, and to provide an effective leaving group with simultaneous protection of the amine, an alternative strategy was followed. Treatment of Boc or Cbz protected phenyl glycinols (**11** or **19**) with $SOCl_2/Et_3N$ provided 1,2,3-oxathiazolidine-2-dioxide **20a**,**b** in good yield (*ca.* 80%). Interestingly, during a scale-up run the oxazolidinone **16** was generated once again, as well as the dimer **21** in considerable amounts.[6] However, with appropriate choice



Scheme 4

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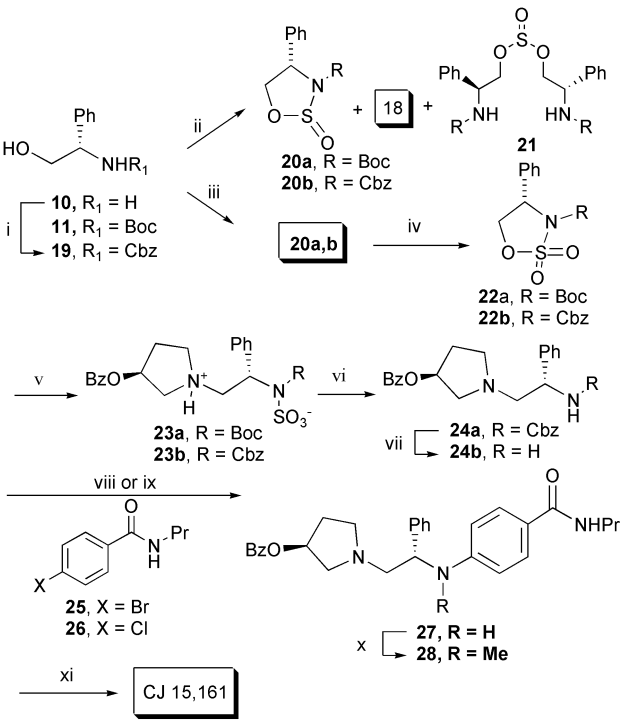
of the base and reaction conditions these impurities were nearly eliminated. Thus, substituting pyridine for triethylamine and with reverse addition of the amine to $SOCl_2$, the isolated yield of **20** increased significantly (~98%). A variety of oxidation conditions were screened for the oxidation of **20** to **22** to avoid decomposition due to over oxidation, partial deprotection (*e.g.*, Boc), or hydrolytic cleavage (Scheme 5). Among them, $NaIO_4$/$RuCl_3$ conditions proved superior, and the desired dioxides **22a**,**b** were isolated in excellent yield (>94%) as off-white solids.

Nucleophilic displacement of the cyclic sulfamidates **22a**,**b** with the benzoate protected pyrrolidinol **6**[7] and removal of protecting groups were straightforward and efficient. Both protected substrates **22a**,**b** coupled easily at room temperature with the aminobenzoate **6**. The sulfamic acids **23a**,**b** could be isolated in 60–70% recrystallized yield as the stable zwitterions; hydrolysis[8] with acid then gave the desired amines **24a**,**b** quantitatively.[9] The Boc protecting group was also removed under these conditions and provided the primary amine **24b** directly. Removal of the Cbz group of **24a** also produced **24b** cleanly under transfer hydrogenation conditions.

A variety of palladium/ligand combinations under a wide range of conditions were explored for the key amination sequence. The palladium-mediated coupling of the benzylamine **24b** with the aryl bromide **25** using a $Pd(OAc)_2$/BINAP catalyst system provided **27** in a modest yield (~39%).[10] Interestingly, the $Pd_2(dba)_3$/(*o*-biphen)P(*t*-Bu)$_2$ combination proved to be effective only when the corresponding aryl chloride **26** was used (*ca.* 42%).[1,2] Reductive alkylation in the presence of paraformaldehyde, using $NaBH_4$/Lewis acids or aqueous formaldehyde/sodium triacetoxyborohydride or NaH_2PO_3 combinations showed some product but the alkylations were not complete even after prolonged reaction time with excess reagent. However, the combination of paraformaldehyde, $NaCNBH_3$, TMSCl and $MgSO_4$ was effective in producing the desired N-methylated product **28** (55%). Since hydrolysis and salt formation of **28** to **1** in one pot has been demonstrated,[11] the present efforts concluded a synthesis of **1**.



Scheme 5 *Reagents and conditions*: (i) CbzCl, CH_2Cl_2, 89%; (ii) $SOCl_2$, Et_3N, CH_2Cl_2, ~80%; (iii) $SOCl_2$, py, CH_2Cl_2, ~90%; (iv) $RuCl_3$, $NaIO_4$, CH_3CN, H_2O, 0 °C to RT, 1 h, >90%; (v) **6**, Et_3N, EtOAc, 60–70%; (vi) 2 M HCl, MTBE; (vii) HCO_2NH_4, Pd/C, THF, quant.; (viii) $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 100 °C, 39%; (ix) $Pd_2(dba)_3$, (*o*-biphen)P(*t*-Bu)$_2$, Cs_2CO_3, toluene, 100 °C, 42%; (x) $(CHO)_n$, $NaCNBH_3$, TMSCl, $MgSO_4$, 55%; (xi) aq. NaOH, IPA, then benzoic acid, 81%.

In summary, we have developed an efficient synthesis of CJ-15,161 involving Pd-catalyzed aryl amination as the key-step. The described approach is amenable for multigram-scale preparation of **1**. The direct amination of 4-halobenzamide[12] as the halide counterpart, and efficient preparation of the substrate amine by dual protection/activation involving oxathiazolidine formation are two noteworthy transformations of the synthetic scheme and may find broader application for the preparation of other N-aryl 1,2-diamines.

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