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Stereocontrolled Syntheses of Epimeric 3-Aryl-6-phenyl-1-oxa-7-azaspiro[4.5]decane NK-1 Receptor Antagonist Precursors

Janusz J. Kulagowski,* Neil R. Curtis, Christopher J. Swain, and Brian J. Williams

Department of Medicinal Chemistry, Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Harlow, Essex, CM20 2QR, UK

janusz_kulagowski@merck.com

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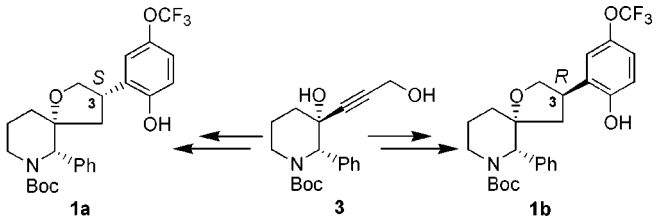
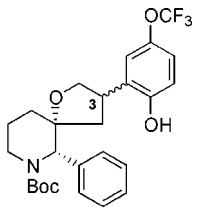
ABSTRACT



Complementary stereoselective syntheses of individual C3 epimers of the NK-1 receptor antagonist precursor 1 have been developed. Both diastereomers were derived from the common intermediate 3; introduction of the 3*S* stereocenter in 1a was achieved through hydrogenation of an arylated dihydrofuran, whereas the corresponding stereogenic center in 1b was installed using a stereo- and regioselective alkene hydroarylation.

The search for clinically useful modulators of the neurokinin NK-1 receptor has remained an active area of inquiry within the pharmaceutical industry[1] since disclosure of the first non-peptide antagonist.[2] Further interest has recently been stimulated by the observation of antidepressant activity through a novel mechanism of action during clinical trials by Merck of an NK-1 antagonist.[3]

Our interest in the area led to a requirement for quantities of both C3 epimers of the 6-phenyl-1-oxa-7-azaspiro[4.5]-decane derivative **1** as precursors to a series of conformationally restricted ligands.[4]



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To ensure a sufficient supply of material for further investigation, it was decided at the outset to develop separate, but parallel, routes to both individual epimers. Under these circumstances, introduction of the C3 stereocenter at a late

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stage in the sequence would offer the most versatile and efficient strategy. Retrosynthetic analysis (Figure 1) suggested that control of this stereocenter could be achieved through appropriate manipulation of the double bond in an unsaturated spiro-piperidine (**2**).

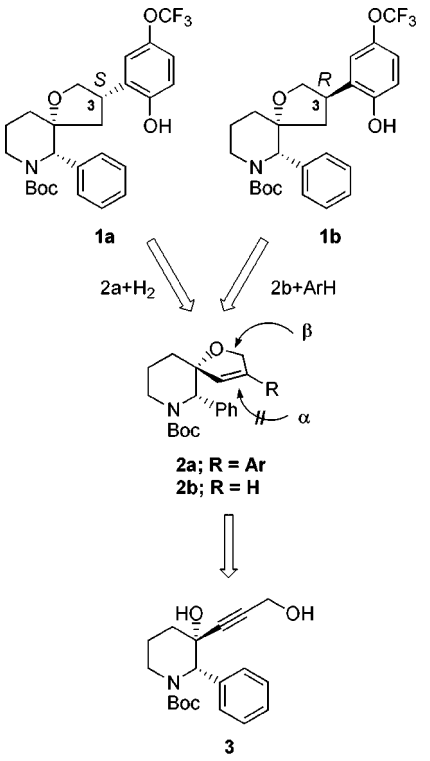
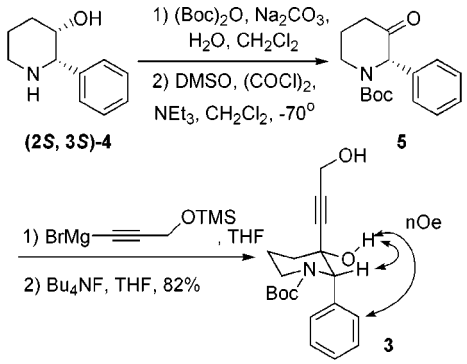


Figure 1. Retrosynthetic approach to individual C3 epimers of **1**.

The *N*-Boc group and pseudoaxially disposed phenyl on the piperidine would be expected to effectively shield the underside of the dihydrofuran, thereby directing approach of reactants to the opposite, *β*-face of the alkene. Thus, hydrogenation of **2a**, in which the double bond bears a suitably substituted aryl group, would give rise to the 3*S* epimer; conversely, the 3*R* diastereomer would be obtained through addition of ArH to unsubstituted alkene **2b**. Furthermore, it was envisaged that the complementarity of the two routes would result in convergence to a common precursor, namely, propargyl diol **3**. Here again, the phenyl group might be expected to exert a controlling influence on the emerging quaternary stereogenic center. In this Letter, we describe the successful implementation of this strategy, resulting in simple, stereocontrolled syntheses of the individual epimers of **1**.

2-Phenylpiperidinol **4** has previously been resolved and used to prepare a series of NK-1 ligands, demonstrating that enantiospecific affinity for the receptor resides with the antipode having the (2*S*) configuration.[5] Accordingly, enantiomerically enriched (>99% ee) (2*S*,3*S*)-(+)-**4** was protected as the *tert*-butyl carbamate and oxidized to ketone **5** under Swern conditions (Scheme 1).

Scheme 1



HPLC analysis of **5** (Chiralpak AD column with 99:1 isohexane/ethanol as mobile phase) indicated no loss in optical purity relative to **4**. Addition of the Grignard derivative of trimethylsilyl propargyl ether proceeded stereospecifically, *anti* to the 2-phenyl group as expected, giving diol **3** in 82% yield from **4** after desilylation. The stereochemical assignment was confirmed by the observation of NOE interactions as indicated, and the enantiomeric integrity of **3** was ascertained by HPLC (>99% ee; Chiralpak AD, 98:2 isohexane/ethanol). The presence of residual **5** in the addition reaction, irrespective of the stoichiometry of Grignard reagent used, suggested that some enolization of the ketone had occurred under the reaction conditions. Recovered ketone was determined to be racemic, indicating that deprotonation had occurred at C2.

Synthesis of the 3*S* epimer (**1a**) continued with palladium(0)-mediated hydrostannylation[6] of **3** (Scheme 2), to provide a mixture of vinyl stannanes (**6a**,**b**) with 7:1 selectivity for the desired regioisomer (**6a**).

Cyclodehydration of the mixture under Mitsunobu conditions, followed by separation of isomers, proceeded uneventfully to afford **7** in 65% yield. Stille cross-coupling with bromide **8a** gave the key intermediate **2a**. Subsequent hydrogenation over Pearlman's catalyst led to cleavage of the benzyl ether with concomitant reduction of the double bond, resulting in a 12:1 selectivity favoring the desired diastereomer **1a** as judged by NMR analysis.

Our retrosynthetic analysis for the construction of **1b** called for a formal hydroarylation of dihydrofuran **2b**. Such transformations have been reported for certain alkenes when exposed to Heck-type carbopalladation under reductive conditions.[7] The success of this strategy rests with the inability of the intermediate *σ*-palladium species to undergo *syn β*-hydride elimination, instead being intercepted by

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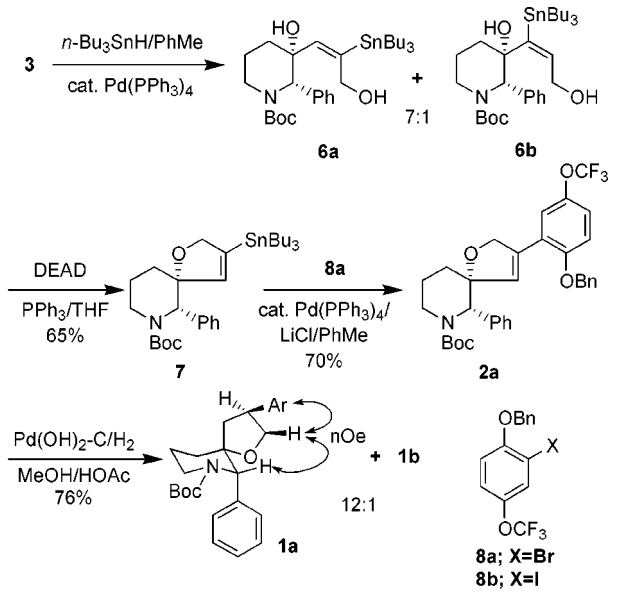
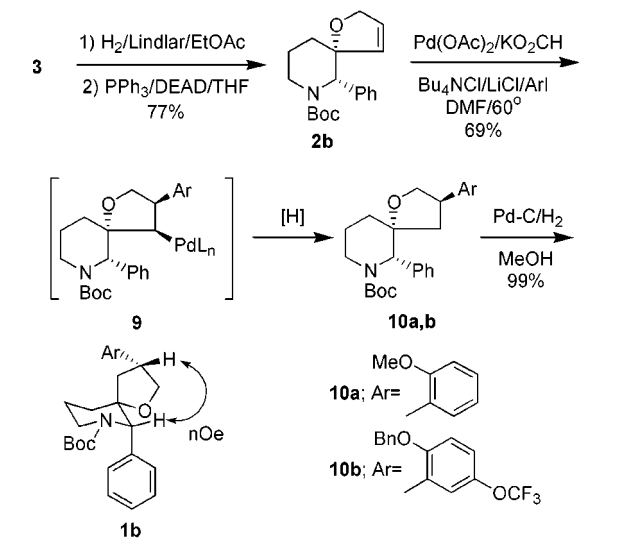
Scheme 2



hydride. In the case of **2b**, steric considerations[8] suggested that *cis* addition of an arylpalladium complex across the double bond would result in intermediate **9** (Scheme 3),

Scheme 3

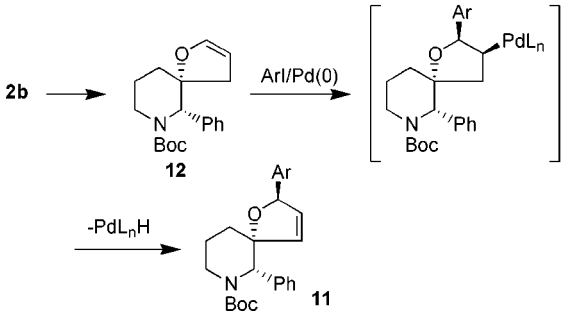


containing the correct regio- and stereochemistry required for **1b** and lacking a *syn* hydrogen adjacent to the palladium.

Encouraged by the prospect of success, **2b** was prepared (Scheme 3) by partial hydrogenation of **3** over Lindlar catalyst, followed by cyclization as before. Attempted coupling with 2-bromoanisole as a model substrate under conditions reported by Larock[9] (cat. $Pd(OAc)_2$, 1 equiv of *n*-Bu_4NCl, 3 equiv of KO_2CH, DMF, rt) resulted in none of the desired arylated material. Instead, only unchanged **2b** accompanied by anisole was observed, indicating that the arylpalladium intermediate was being intercepted by hydride prior to addition to **2b**. In contrast, 2-iodoanisole did lead to the desired coupling, giving **10a** in a modest 10% yield, although again accompanied by anisole as the major product. An investigation of reaction parameters was undertaken with the aim of optimizing the desired coupling reaction. While turnover was very slow at ambient temperature, performing the reaction at 80 °C resulted in rapid deposition of colloidal palladium accompanied by termination of the reaction. Different formate counterions, as well as tertiary amines,[10] were evaluated as reductants. Additives such as triarylphosphines, triphenylarsine,[11] or silver salts[12] appeared to suppress the reaction, while use of the corresponding aryl triflate failed to give significant conversion. These studies eventually led to adoption of the following optimized conditions: 0.1 equiv of $Pd(OAc)_2$, 1 equiv of *n*-Bu_4NCl, 3 equiv of KO_2CH, 3 equiv of 2-iodoanisole, 10 equiv of LiCl, DMF, 60 °C. The inclusion of excess chloride ions, most conveniently as the lithium salt, was found to be beneficial in suppressing competing reduction of starting aryl iodide, although the mechanism underlying this observation is presently unclear.[13] Application of these conditions to the reaction of **2b** with **8b** gave **10b** in 69% yield as a 20:1 mixture with the corresponding 3*S* isomer. Hydrogenolysis provided **1b**, which was confirmed as having the 3*R* configuration by the presence of an NOE interaction between the two benzylic protons.

A further product observed in the hydroarylation reaction was the unsaturated regioisomer **11**, isolated in 12% yield. Formation of this material may be rationalized by initial isomerization of **2b** to the enol ether **12** followed by α-arylation and subsequent *β*-elimination of the palladium (Scheme 4).[14]

Scheme 4



In summary, we have developed simple, stereocontrolled syntheses of both C3 epimers of 3-aryl-6-phenyl-1-oxa-7-azaspiro[4.5]decane, **1a** and **1b**. The complementarity of the

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two routes allows use of a common intermediate (**3**) to provide multigram quantities of precursors to conformationally restricted NK-1 antagonists.

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Supporting Information Available: Experimental procedures and characterization data for compounds **1a**, **1b**, **2a**, **2b**, **3**, **5**, **7**, **8a**, **8b**, **10b**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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