JOC Article

A Practical and Scaleable Synthesis of A-224817.0, a Novel Nonsteroidal Ligand for the Glucocorticoid Receptor†

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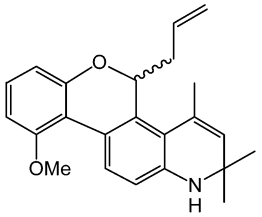
Received December 17, 2002

A practical and scaleable synthesis of a novel nonsteroidal ligand for the glucocorticoid receptor A-224817.0 **1A** is described. The synthesis proceeds in seven steps starting from 1,3-dimethoxybenzene. The biaryl intermediate **5** was prepared by an optimized high-yielding and high-throughput Negishi protocol. The quinoline core **8** was constructed by using a modified Skraup reaction. The final product was obtained by a direct allylation reaction of lactol **10** with allyltrimethylsilane. The process was accomplished efficiently to produce **1A** in 25% overall yield and >99% purity with simple and practical isolation and purification procedures.

Introduction

Glucocorticoids[1] therapy has been used for the treatment of inflammatory diseases for more than forty years. Synthetic glucocorticoids such as dexamethasone[2] and prednisolone[3] have been widely used in the clinical treatment of chronic inflammatory diseases. It is also well documented that corticosteroid antiinflammatory therapy causes many undesirable side effects, such as glucocorticoid-induced osteoporosis[4] and glucose intolerance.[5] These side effects occur because these glucocorticoids have cross-reactivity with other steroid receptors.[6,7] Medicinal chemistry research sought after a nonsteroidal glucocorticoid receptor selective ligand that would imitate natural glucocorticoids but differentiate from the metabolic side effects.[8,9]



1A. A-224817.0 (Racemate)
1B. A-240610.0 (S-enantiomer)

A-240610.0 **1B**,[10,11] the *S*-enantiomer of A-224817.0 **1A**,[8,9] has demonstrated equivalent antiinflammatory activity relative to prednisolone with an improved side effect profile in vivo. To further evaluate its effectiveness, an efficient process, which is suitable for large-scale preparation, was required to prepare a larger quantity of material to support initial biological studies. Thus, a practical and scaleable seven-step chromatography-free process was developed for the preparation of A-224817.0 **1A**.

Results and Discussion

Preparation of the biaryl compound **5** was initially accomplished with a two-step process[8] with an overall yield of 58%, using a Suzuki protocol[12] (Scheme 1) in which the isolated boronic acid **3** was coupled in the

† This article is dedicated to the memory of 100 year old Emeritus Professor Y. H. Ku of the University of Pennsylvania, who passed away on September 9, 2002.

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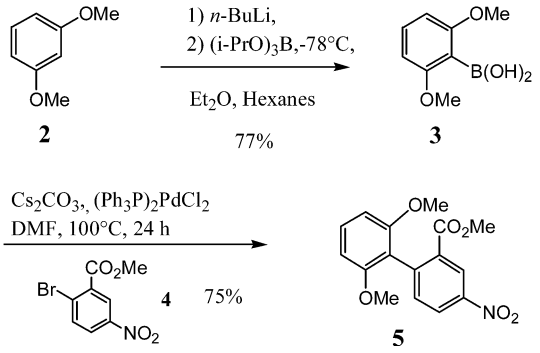
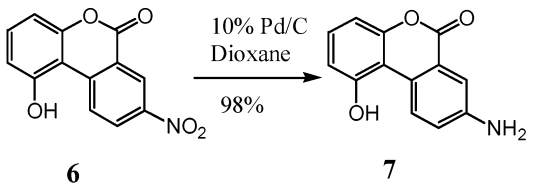
10.1021/jo0268613 CCC: $25.00
Published on Web 03/20/2003

SCHEME 1



SCHEME 2



presence of Pd-catalyst with 2-bromo-5-nitrobenzoate **4** at 100 °C in DMF. The concerns with its low overall yield, long processing time, and tedious isolation and purification procedures have led to the development of a highly efficient alternate Pd-catalyzed cross-coupling procedure involving a Negishi protocol[13] (Scheme 4). This procedure involves lithiation of 1,3-dimethoxybenzene **2** with *n*-BuLi at 0 °C in THF followed by transmetalation with $ZnCl_2$ to generate the organozinc derivative in situ. It was then coupled directly with 2-bromo-5-nitrobenzoate **4** in the presence of a palladium catalyst, dichlorobis-(triphenylphosphine)palladium, to produce the desired biaryl compound **5** in essentially quantitative conversion. The reaction went to completion within 2 h and the product precipitated out of the reaction mixture, which simplified the isolation and purification. The desired product was isolated in excellent yield (90%) and high purity (99%) by a simple filtration.

The biaryl **5** was then treated with boron tribromide in a two-step, one-pot protocol [8] in which cleavage of the methoxy groups was followed by lactone formation to yield nitrocoumarin **6** in 93% yield (Scheme 4). Initially, the reduction of the nitrocoumarin **6** to the aminocoumarin **7** was carried out by hydrogenation with palladium on carbon in dioxane (Scheme 2). Although the reduction worked well, large volumes of solvent and long reaction times (over 40 h) were required due to the poor solubility of the nitrocoumarin **6** in dioxane. A hot filtration of the reaction mixture to remove palladium catalyst was also necessary to prevent the product from precipitating out of the solution. In addition, isolation of the product from a water−dioxane suspension involved a slow filtration during which some product degradation occurred. Furthermore, dioxane as a solvent was not desirable due to its hazardous nature. Solubility studies with a variety of solvents revealed that the starting material, nitrocoumarin **6**, and product, aminocoumarin **7**, were both highly soluble in NMP (1-methyl-2-pyrrolidinone). By changing

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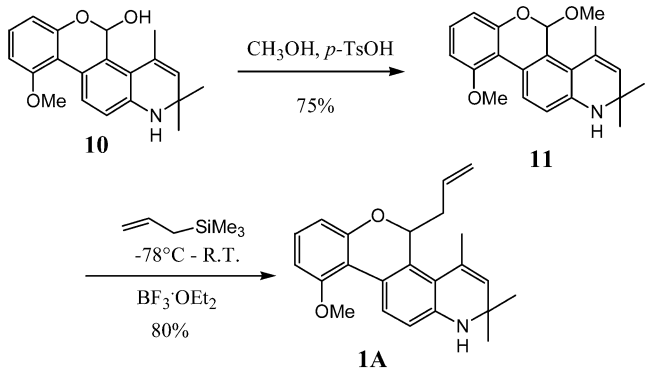
SCHEME 3



the reaction solvent to NMP, the reaction concentration was increased 10-fold. The reaction time was reduced from 40 h to less than 2 h. Removal of Pd-catalyst could then be carried out at room temperature. It was also found that the filtered reaction mixture could be used directly in the next step, thus, the isolation step was eliminated. This modification improved the throughput 10-fold. In addition, the decomposition of the isolated aminocoumarin **7** intermediate was avoided.

The Skraup reactions[14] have been demonstrated as efficient routes for assembling quinolines. The quinoline core **8** was constructed by the modified Skraup reaction with use of the published protocol[15] with some variations (Scheme 4). The reaction was performed in acetone/NMP in the presence of iodine at high temperature (105 °C) and pressure for 72 h. The presence of NMP allowed the reaction to be carried out in higher concentration. Initially, a tedious column chromatography that required large volume of solvents[8] was needed to purify the quinoline core **8**. It was observed that the desired product was quite soluble in EtOAc/heptane, while the polymeric byproducts were not. Thus an improved isolation and purification procedure was developed involving an extractive workup procedure. The majority of the byproducts were removed with a liquid−liquid extraction of EtOAc/heptane and H_2O followed by a filtration. The purity of the isolated product could be further improved by formation of an HCl salt. The quinoline core **8** was methylated with dimethyl sulfate in the presence of potassium *tert*-butoxide in THF to give the methylated quinoline lactone **9** in 89% yield (Scheme 4). The lactone **9** was then reduced with DIBAL[16] in toluene to produce the lactol **10** in 79% yield.

The final product A-224817.0 **1A** was prepared initially by a two-step reaction sequence[8] from the lactol **10**: methylation of lactol **10** in methanol in the presence of p-TsOH to produce the methyl lactol **11** and allylation with allyltrimethylsilane (Scheme 3). This reaction sequence was demonstrated to work well although chromatographic purification of both methyl lactol **11** and the final product **1A** were required.

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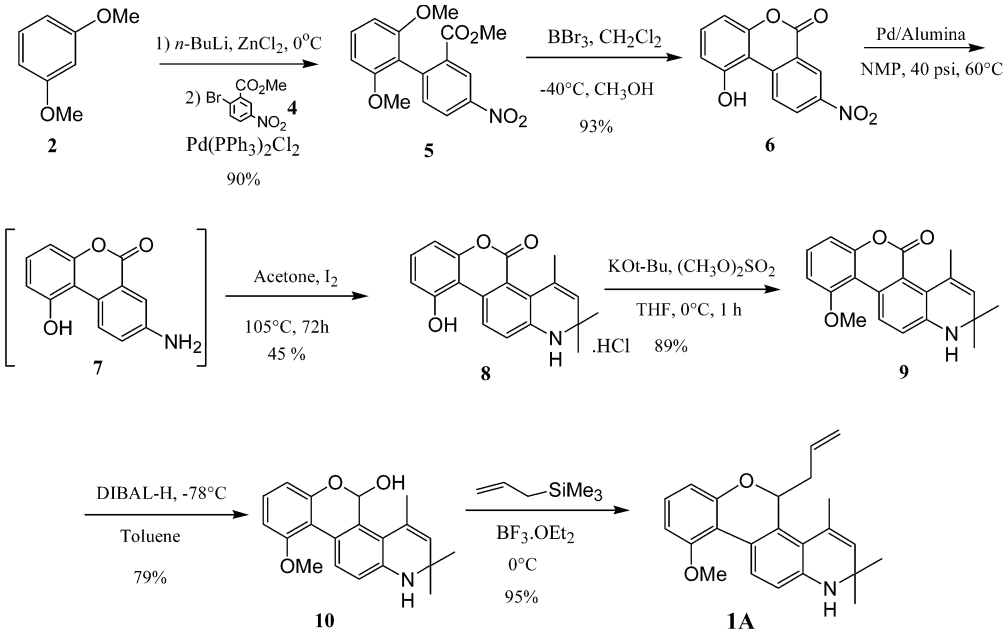
SCHEME 4



It was then discovered that the lactol **10** could be directly allylated with allyltrimethylsilane after being purified by crystallization with EtOAc/heptane to produce the final compound A-224817.0 **1A** in excellent yield (95%) and purity (96%). The reaction could be carried out at 0 °C instead of −78 °C under 3-fold concentrated conditions, using fewer equivalents of reagents (2 instead of 4 equiv). Initially the final product **1A** was isolated as a foam; it was critical to obtain a crystalline solid for the final product that would allow the isolation and purification procedure to be more practical. After screening a variety of solvent and solvent combinations, polar solvents, such as EtOH or ^{i}PrOH, were found to effectively crystallize the final product. This made the isolation and purification of the final product practical and efficient, thus crude allylation product **1A** could be further purified to high purity (>99%) by simple crystallization and filtration.

In summary, we have developed an efficient, practical, and scaleable process for the synthesis of A-224817.0 **1A** as a crystalline solid with an overall yield of 25% in high purity (>99%). The process is highlighted by the development of a highly efficient Pd-catalyzed cross-coupling reaction for the preparation of the biaryl intermediate **5** and a direct allylation procedure to allylation of lactol **10**. In addition, the ability to obtain a crystalline solid for A-224817.0 **1A** made the isolation and purification of the final product simple and practical. This column chromatograph-free process has addressed several concerns related to the scale-up of chemical processes and is amendable to the large-scale preparation of A-224817.0 **1A**.

Acknowledgment. The authors would like to thank Phil Kym, Steve Elmore, and Mike Coughlan of Medicinal Chemistry for their assistance and useful discussions.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0268613