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A practical and efficient synthesis of 6-carboalkoxy-13-cycloalkyl-5*H*-indolo[2,1-*a*][2] benzazepine-10-carboxylic acid derivatives

Piyasena Hewawasam *, Yong Tu, Thomas W. Hudyma, Xiaofan Zhang, Robert G. Gentles, John F. Kadow, Nicholas A. Meanwell

Department of Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research and Development, 5 Research Parkway, Wallingford, CT 06492, United States

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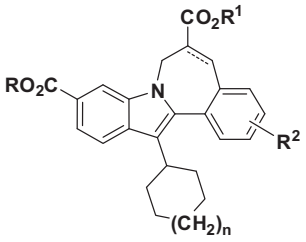
ABSTRACT

A convenient and practical synthesis of 6-carboalkoxy-13-cycloalkyl-5*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid derivatives (**6**) has been developed. The key step in the synthesis utilizes an intramolecular tandem reaction sequence of a Michael addition followed by a Horner–Wadsworth–Emmons (HWE) olefination reaction between hemi-aminal **11** and methyl 2-(dimethoxyphosphoryl)acrylate **12**. The ring construction occurred efficiently and purification of the products **6** was straightforward. The C-10 methyl ester of **6a** was hydrolyzed selectively to the carboxylic acid **13** while the olefin of **6d** was converted to the cyclopropane **14** using trimethylsulfoxonium iodide in DMSO in the presence of NaH.

Introduction

We have recently described the synthesis and evaluation of a series of bridged 2-arylindole-based non-nucleoside hepatitis C virus (HCV) non-structural protein 5B (NS5B) RNA-dependent RNA polymerase inhibitors that bind to thumb site 1 of the enzyme.[1–4] Compound **2** (Scheme 1) is a representative prototype that demonstrates antiviral activity in a genotype 1b HCV replicon with an EC_{50} of 0.84 μM.[1] The 3-carbon atom bridge of **2** was assembled from the acyclic precursor **1** using a ring closing metathesis (RCM) reaction effected by the Grubbs 2nd generation catalyst, as depicted in Scheme 1.[1,5–7] Other bridge elements examined include the amide **3**, EC_{50} = 0.07 μM, the ether **4**, EC_{50} = 0.69 μM, and the fused benzodiazonine **5**, EC_{50} = 0.60 μM.[1] The potency advantage offered by the amide linker in **3** was attributed to interactions between the amide moiety and the polymerase enzyme rather than to an effect of the linker on the dihedral angle between the 2-phenyl substituent and the indole core, established as a factor contributing to inhibitory potency.[1]

As part of the evolution of this chemotype toward compounds with enhanced potency, we sought to explore linkers in which polar functionality was appended to the bridge element rather than integrated within it as in **3** and which would provide vectors suitable for further probing of the interactions between inhibitor and enzyme. To that end, 6,10-disubstituted indolo[2,1-*a*][2]benzazepines of general structure **6** were considered for examination since the ester moiety at C-10 and the olefin at C-10-C-11 provided functionality convenient for further elaboration.[6]



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The indolo[2,1-*a*][2]benzazepine ring system is sparsely represented in the literature prior to the advent of the HCV NS5B thumb site inhibitor chemotype represented by **2**.[6,7] The initial approach adopted to access fused indoles **6** relied upon a ring-closing metathesis reaction analogous to that used to prepare **2**, a procedure summarized in Scheme 2. Suzuki coupling[8] of 2-vinylphenylboronic acid (**8**) with methyl 2-bromo-3-cyclohexyl-1*H*-indole-6-carboxylate (**7**) afforded the 2-phenyl indole **1** which was alkylated with methyl 2-(bromomethyl)acrylate using NaH as base in DMF to give **9**. A RCM approach was successful in providing **6a** but this procedure gave low and variable yields and purification typically required extensive chromatography.[5] Moreover, due to the high dilution requirements, extended reaction times, and the expense associated with both the 2-vinylphenylboronic acid (**8**) starting

* Corresponding author. Tel.: +1 203 677 7815.
E-mail address: Piyasena.Hewawasam@bms.com (P. Hewawasam).

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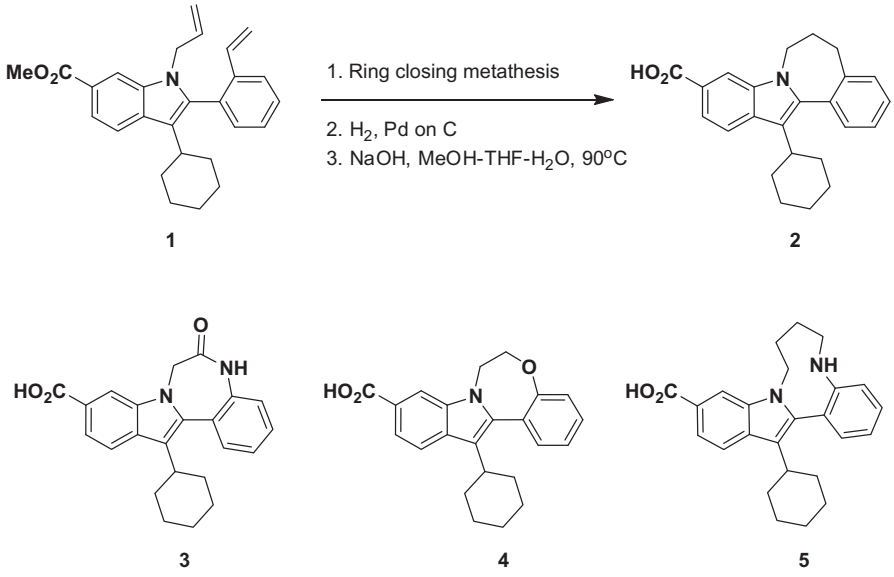
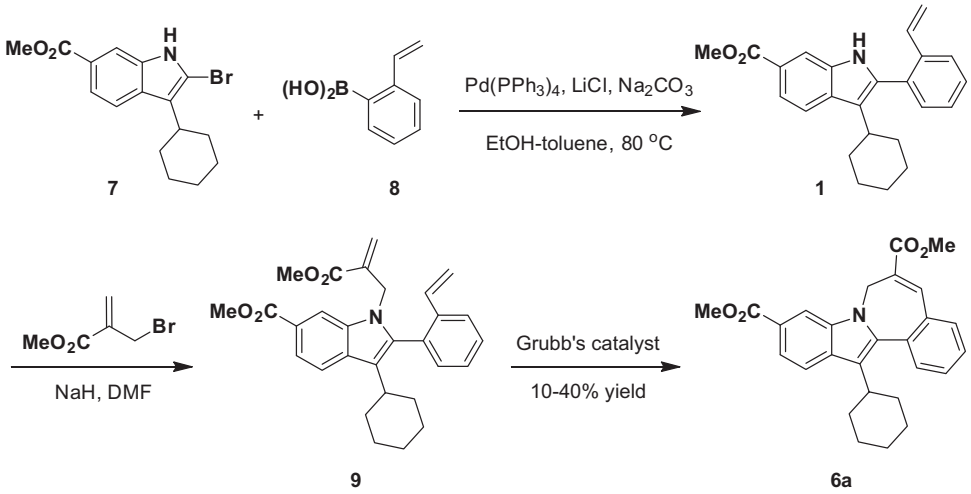
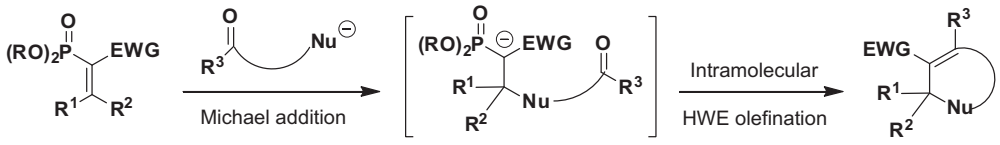


Scheme 1.



Scheme 2.



Scheme 3.

material and the RCM catalyst, scale-up presented concerns of both a practical and economical nature. As a consequence, we sought an alternative and a more reliable synthetic approach to the preparation of **6a** and its analogues.

A tandem Michael addition-Horner–Wadsworth–Emmons (HWE) ring closure process, captured in Scheme 3, was considered as a synthetic approach with the potential to deliver **6** from readily available and less expensive reagents.[9,10] This process envisages the use of an activated vinylphosphonate reacting as a Michael acceptor with the indole nitrogen as the nucleophile, a process anticipated to be facilitated in the case at hand by the C-6 electron withdrawing group while the cyclohexyl moiety would retard reaction at C-3, which is often favored with unsubstituted indole substrates.[11] Vinylphosphonates containing electron-withdrawing groups (EWGs) at the α-position, such as alkoxycarbonyl, carbonyl, cyano, sulfinyl, sulfonyl, or phosphoryl groups are reactive electrophiles that have found useful application in organic synthesis.[9,10] A phosphoryl group not only facilitates the Michael addition but also enables a subsequent HWE olefination of carbonyl moieties which can be presented either inter- or intra-molecularly.[9–11]

The construction of the 5*H*-indolo[2,1-*a*][2]benzazepine ring system using this approach required the aldehyde **11**, readily prepared from the 2-bromoindole **7** and 2-formylphenylboronic acid