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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

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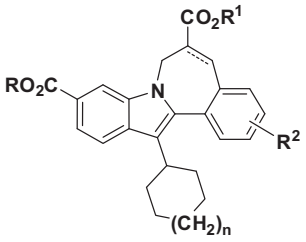
ABSTRACT

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]



6

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

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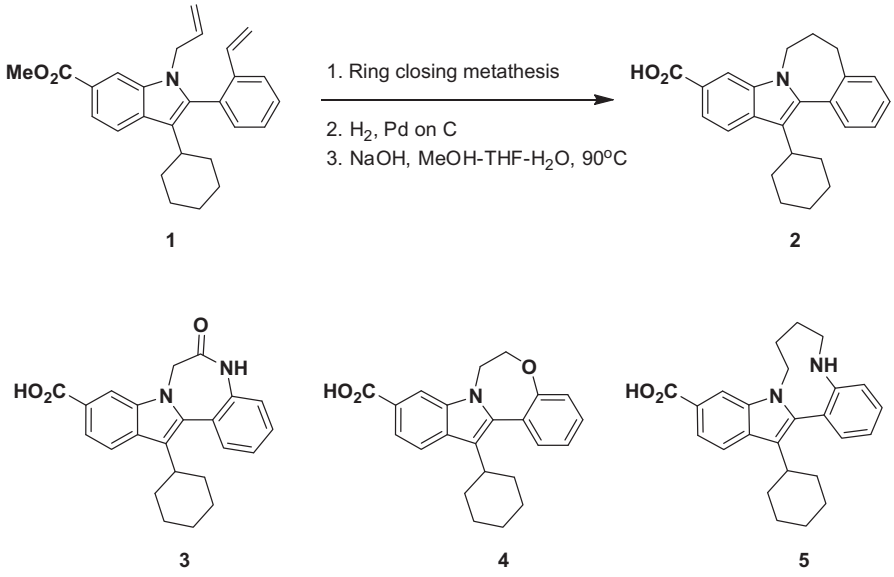
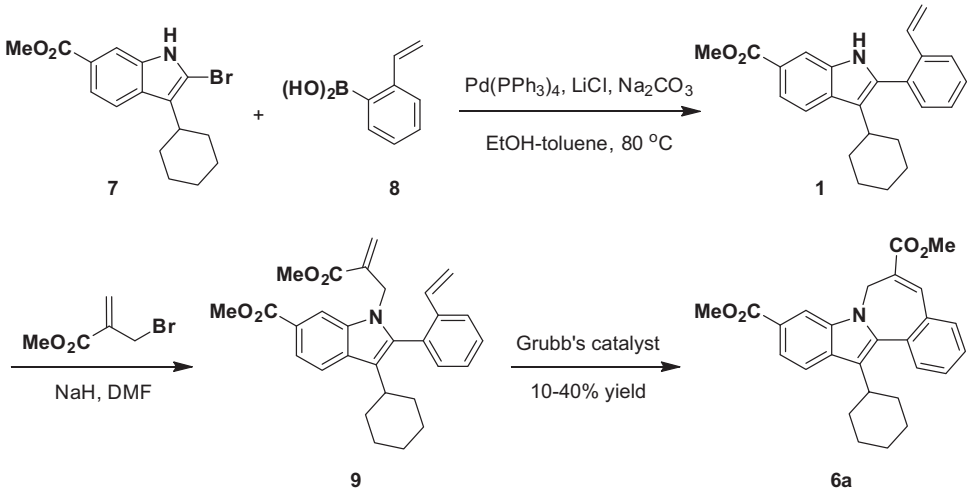
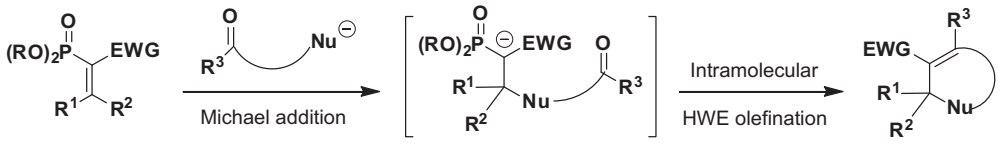


Scheme 1.



Scheme 2.

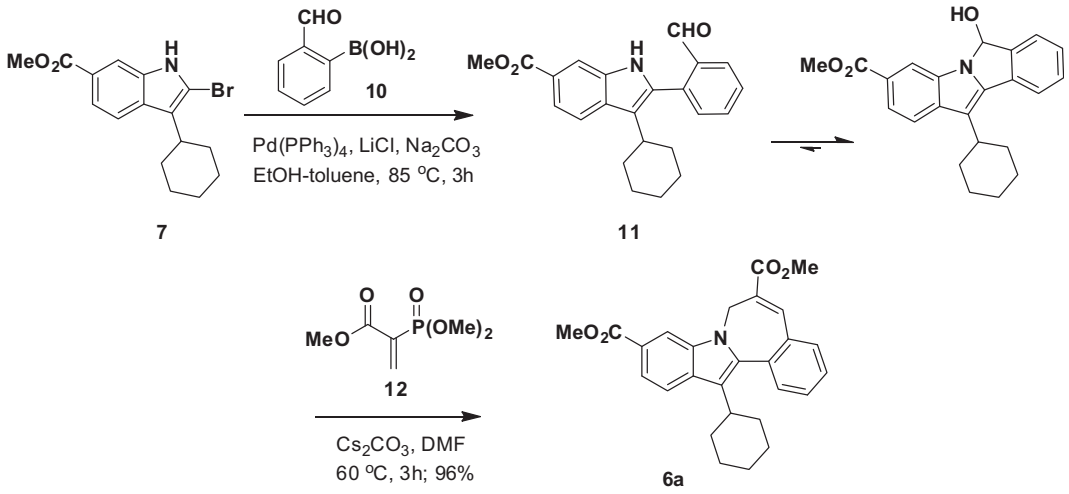


Scheme 3.

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



Scheme 4.

(**10**) via a Suzuki reaction (Scheme 4). 2-Formylphenylboronic acid (**10**) is commercially available and over 50-fold less expensive than 2-vinylphenylboronic acid (**8**) which was used in the RCM approach described in Scheme 1. Interestingly, aldehyde **11** exists primarily in the closed, hemi-aminal form also depicted in Scheme 4. Gratifyingly, heating a mixture of **11**, methyl 2-(dimethoxyphosphoryl)acrylate (**12**), and Cs_2CO_3 in DMF at 60 °C under an atmosphere of N_2 for 3 h smoothly effected a tandem Michael addition-HWE ring closure to afford **6a** in 96% yield after a simple filtration (Table 1, entry 1). The phosphoryl moiety of **12** was found to

Table 1
Substrate, products, and yields for the tandem Michael addition-HWE ring closure protocol to afford 6-carboalkoxy-13-cycloalkyl-5*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid derivatives

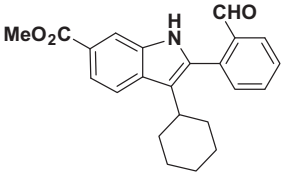
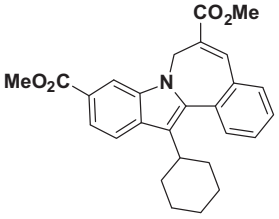
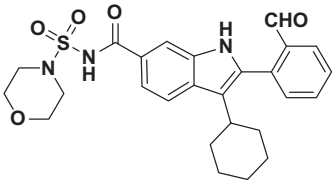
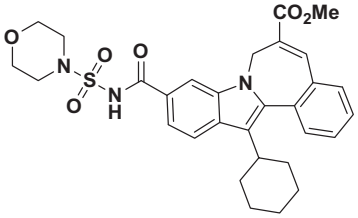
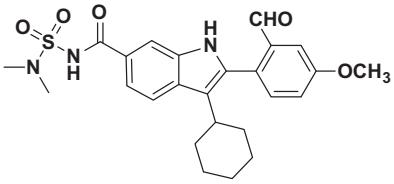
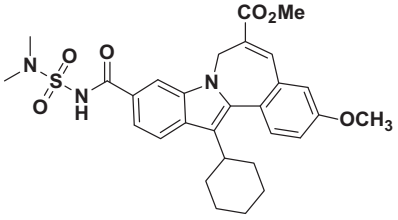
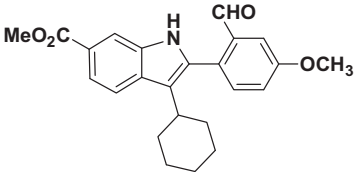
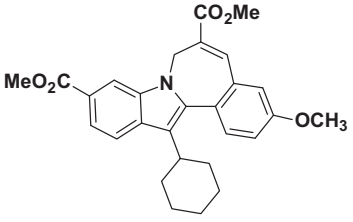
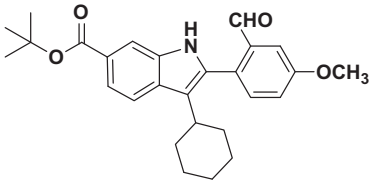
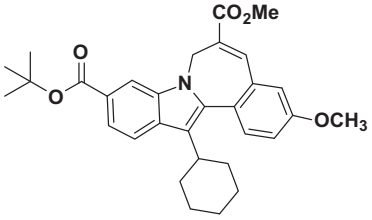
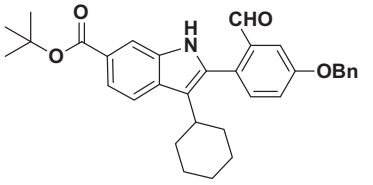
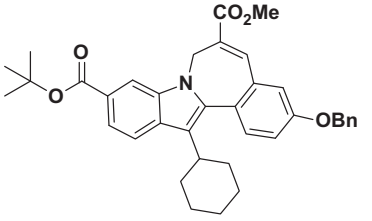
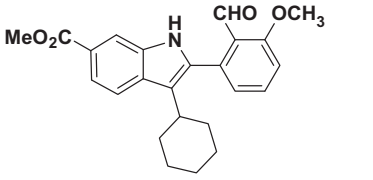
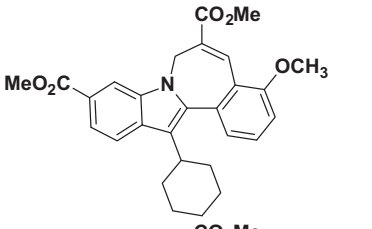
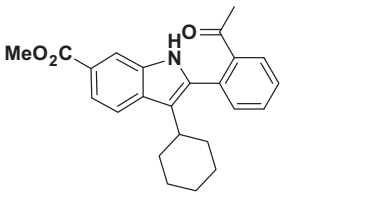
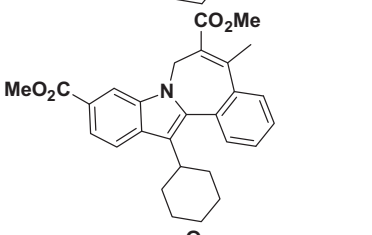
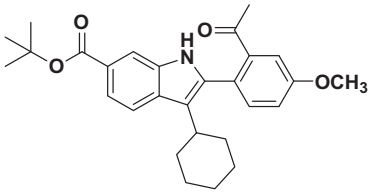
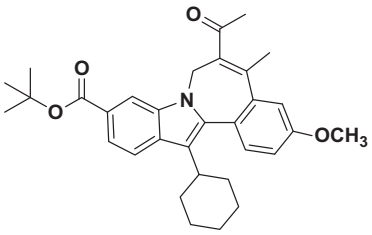
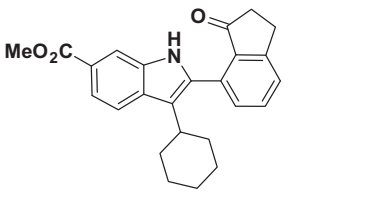
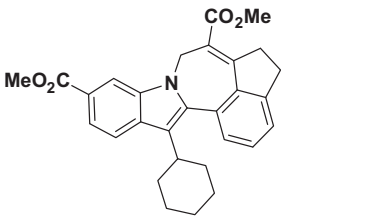
Entry #	Substrate	MA-HWE product	Yield
1	**11a** 	**6a** 	96%
2	**11b** 	**6b** 	81%
3	**11c** 	**6c** 	72% over 2 steps
4	**11d** 	**6d** 	97% on a 2.9 g scale — gave 3.3 g

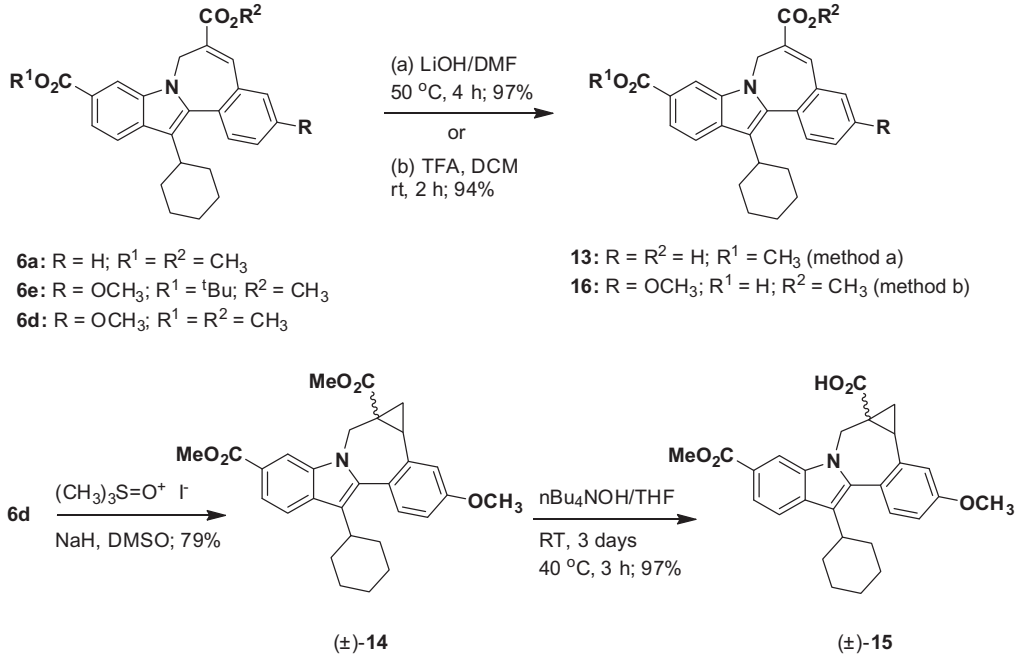
Table 1 (*continued*)

Entry #	Substrate	MA-HWE product	Yield
5	**11e** 	**6e** 	90% on a 70 g scale
6	**11f** 	**6f** 	95% on a 32.5 g scale — gave 35 g product
7	**11g** 	**6g** 	89%
8	**11h** 	**6h** 	80%
9	**11i** 	**6i** 	54%
10	**11j** 	**6j** 	0%

be essential for a successful outcome since the reaction of indole **11** with methyl acrylate provided a Michael adduct that could be induced to undergo a Knoenvenagel reaction to afford **6a** in yields that never exceeded 27% with considerable recovery of the uncyclized ester.[12,13]

Several additional examples of this ring closing procedure are compiled in Table 1. The protocol is compatible with the presence of the acidic functionality present in **11b** and **11c** (Table 1, entries 2 and 3) and is effective with the electron rich aldehydes **11c–g** (Table 1, entries 3–7) including the sterically encumbered aldehyde **11g** depicted in entry 7. Ring closure onto a ketone carbonyl, exemplified by the acetophenones **11h** and **11i** (Table 1, entries 8 and 9), also occurred in modest to good yield. However, the indanone substrate **11j** (Table 1, entry 10) failed to provide isolable product, attributed to an inability of the intermediate phosphonate-stabilized anion to approach the ketone on a suitable trajectory for reaction.[14]

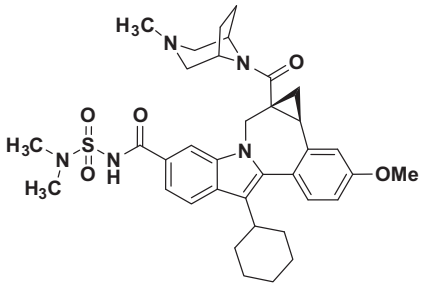
In order to further elaborate **6a**, selective hydrolysis of the C-10 ester moiety to give **13** was accomplished in 97% yield by treatment with LiOH in DMF at 50 °C for 4 hours (Scheme 5). Cyclopropanation of the olefin of **6d** was accomplished by exposure to trimethylsulfoxonium iodide in DMSO in the presence of NaH as the base to afford racemic **14** in 79% after chromatography.[15] The ^{1}H NMR spectral data are consistent with **14** existing as a mixture of rapidly converting atropisomers. Selective hydrolysis of the C-10 ester of **14** using nBu$_4$NOH in THF gave the acid **15** in 97% yield



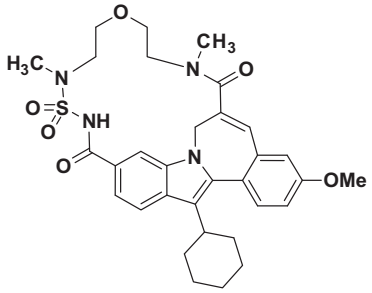
Scheme 5.

after an extractive work up. The C-6 *t*-butyl ester moiety of **6e** could be removed selectively under acidic conditions to give **16**. These protocols for selective functionalization of **6** facilitated an exploration of structure-activity relationship studies for this class of HCV NS5B inhibitors.[6]

This process proved to be sufficiently robust and reliable that it was employed broadly to produce fused indole core structures in a program that ultimately led to the identification of BMS-791325 (**17**), a potent HCV NS5B inhibitor that is currently in clinical trials as part of combination therapy for the treatment of HCV infection.[16–18] In addition, this Michael addition-HWE protocol has been adopted to access a series of structurally-related macrocyclic HCV NS5B inhibitors that gave rise to TMC-647055 (**18**), a compound undergoing clinical evaluation.[19–21]



17 (BMS-791325)



18 (TMC-647055)

Conclusions

We have described the development of a practical, effective, and economical approach to the 5*H*-indolo[2,1-*a*][2]benzazepine ring system that does not depend on expensive catalysts or reagents. The process is operationally straightforward and the product of the key Michael addition-Horner–Wadsworth–Emmons ring forming process is readily isolated in high purity in the case of the prototypical compound **6a**. The method is amenable to multigram preparative scale (we have conducted this process on scales ranging up to 1 kg) and, in principle, a variety of functional groups could be incorporated at C-10 using this methodological approach. The C-10 methyl ester of the **6a** can be hydrolyzed selectively in the presence of the C-6 methyl ester.

Supplementary data

Supplementary data (experimental protocols for the preparation of compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.085.

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