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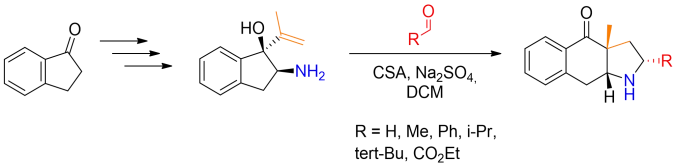
Synthesis and antiviral activity of tricyclic cis-fused pyrrolidines

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Novel tricyclic cis-fused pyrrolidines were synthesized via a key tandem aza-Cope rearrangement–Mannich cyclization, enabling efficient construction of the core scaffold. The compounds were evaluated for antiviral activity and cytotoxicity against herpes simplex virus (HSV) and cytomegalovirus (CMV). Two compounds showed moderate anti-CMV activity (IC_{50} ≈ 23 μg/mL) with selectivity indices around 5, highlighting the promise of this scaffold for further optimization.



Keywords: tandem aza-Cope/Mannich, tricyclic pyrrolidine, nitrogen heterocycles, herpes simplex virus, cytomegalovirus.

The development and synthesis of new pharmaceutical agents present numerous challenges for synthetic and medicinal chemists. One key challenge is the design of rational and efficient synthetic methods for biologically active compounds. Of equal importance is the development of approaches enabling stereoselective synthesis, as many natural alkaloids and lead compounds contain asymmetric carbon centers in their structures. Among biologically active alkaloids and synthetic drug candidates, a number of compounds featuring a condensed pyrrolidine moiety can be identified (Figure 1) [1–5].

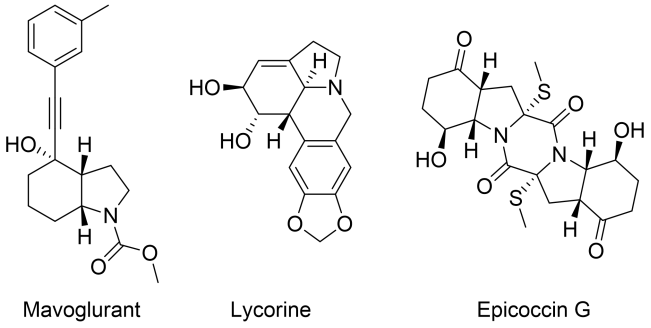


Figure 1 Examples of compounds containing a fused pyrrolidine fragment.

Previously, our research group synthesized a series of diverse compounds containing a condensed pyrrolidine moiety (Figure 2) [6–8]. The antiviral activity of these compounds was studied. To advance this line of research, and motivated by the unmet need for new agents against herpesviruses (HSV-1 and HCMV), where current drugs (acyclovir, ganciclovir, foscarnet) are limited by resistance and toxicity, we proposed modifying the molecular core by introducing an aromatic fragment annulated with the alicycle.This led to the design of a series of tricyclic cis-fused pyrrolidines. Herein, we describe the first synthesis of this scaffold via the tandem aza-Cope–Mannich rearrangement and its preliminary evaluation against herpes simplex virus type 1 and human cytomegalovirus.

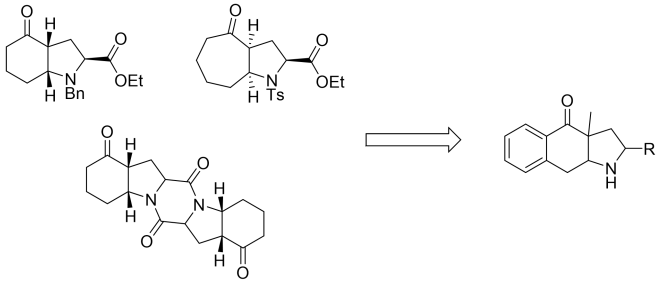
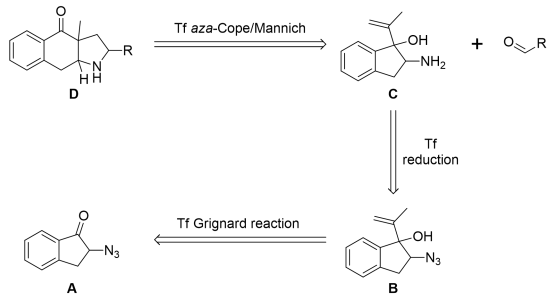


Figure 2 Examples of previously obtained compounds and the general structure of the target compounds in this study.

To synthesize the target tricyclic structures, a retrosynthetic analysis was performed (Scheme 1), which consisted of three stages.

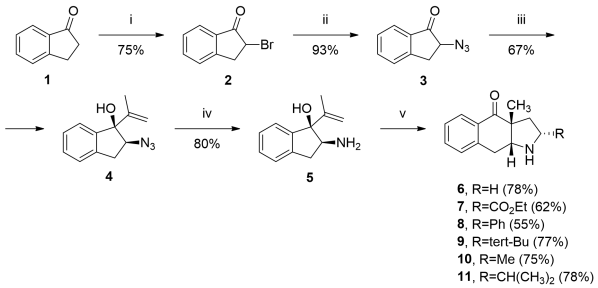
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Scheme 1

The pivotal transformation in our synthetic route is a tandem aza-Cope rearrangement–Mannich cyclization. Consequently, this study began with the synthesis of α-azidoketone precursors (**A**), which were converted to alcohols (**B** and **C**) and thence to the target tricyclic derivatives (**D**). The availability of reagents, relatively mild reaction conditions, high yields, experimental simplicity, and the predictable stereochemical outcome of this transformation were expected to enable the successful synthesis of the required compounds in quantities sufficient for further synthetic transformations.

Retrosynthetic analysis informed a concise synthetic strategy using commercially available ketone (**1**) as starting material, executed through straightforward steps (Scheme 2). Such sigmatropic rearrangements are known to proceed diastereoselectively [9]. Therefore, it was anticipated that, due to spatial constraints in the transition state, this synthetic route to the tricyclic core would proceed with high diastereoselectivity. Moreover, when enantiomerically pure aminoethanols are used, this process can be carried out without loss of enantiomeric purity.



Scheme 2 *Reagents and conditions*:i, Br_2, Et_2O, room temperature, 0-25°C, 8 h; ii, NaN_3, MeCN, room temperature, 8 h; iii, prop-1-en-2-ylmagnesium bromide, anhydrous $CeCl_3$, THF, -78°C, 2 h; iv, $LiAlH_4$, THF, 0°C, 6 h; v, aldehyde, CSA (D-(+)-10-camphorsulfonic acid), Na_2SO_4, DCM (dichloromethane), room temperature, 10 h.

First, commercially available indanone 1 was reacted with bromine in diethyl ether, yielding α-bromoketone **2** in 75% yield. An alternative approach using NBS (N-bromosuccinimide) was attempted but proved less efficient. In the next step, compound **2** underwent nucleophilic substitution with sodium azide, affording the product in 93% yield. It is important to note that this compound is unstable and prone to decomposition; therefore, it must be stored at low temperatures and used promptly. The conditions for this transformation were optimized (Table 1). The use of acetonitrile as the solvent and two equivalents of sodium azide proved most effective.

Table 1 Optimization of the synthesis conditions for indane derivative **3**

Solvent	Equivalents of sodium azide	Concentration, M	Time, h	Yield, %
MeCN	1	1	8	62
DMF	1	1	8	57
DMSO	1	1	8	43
Acetone	1	1	8	51
MeCN	1	1	4	54
MeCN	1	1	12	59
MeCN	1	0.5	8	51
MeCN	1	0.5	12	46
MeCN	1	2	8	42
MeCN	1	2	12	39
MeCN	2	0.5	8	74
MeCN	2	0.5	12	69
MeCN	2	1	8	93
MeCN	2	1	12	85
MeCN	2	2	8	76
MeCN	2	2	12	63

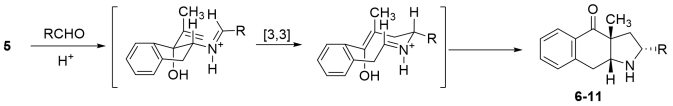
The next step in the synthetic sequence involved the addition of a Grignard reagent to azidoketone **3**. Given our laboratory's extensive experience with similar compounds [7,8], it was decided to use not a classical Grignard reagent but its modification based on generating an organocerium species, which subsequently reacted with compound **3**. This modification was necessary because Grignard reagents are strong bases, while the azide group is a potent electron-withdrawing group. Consequently, such azidoketones readily undergo enolization upon treatment with organomagnesium compounds, and the resulting enol does not participate in the desired reaction. Furthermore, Grignard reagents can reduce the azide group to an amine, and the resulting aminoketone polymerizes, forming a resin. To overcome these issues, organocerium reagents, which possess significantly lower basicity, are used. They are prepared from anhydrous cerium(III) chloride and Grignard reagents [10,11]. This approach was employed in the current work, allowing the synthesis of unsaturated azido alcohol **4** in 67% yield. This reaction resulted in the formation of only one diastereomeric pair.

Subsequently, the azide was reduced with lithium aluminium hydride in THF, yielding the unsaturated amino alcohol **5** in 80% yield. This method proved optimal for the reduction. Other reduction methods were attempted, such as zinc in the presence of ammonium chloride (~50% yield), hydrogen with a palladium on activated carbon catalyst (~50% yield), and Staudinger conditions (~60% yield). The listed alternative methods have several drawbacks, including the formation of byproducts, cumbersome experimental procedures, and more complex purification processes. These alternative reduction methods were less effective for obtaining the required unsaturated amino alcohol.

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The transformation of non-cyclic and cyclic aminoethanols into substituted pyrrolidine and octahy-dro-4H-indol-4-one derivatives was first described in the works of Larry Overman [12–14]. In the case of cyclic amino alcohols (e.g., amino alcohol **5**), this reaction sequence leads to an increase of the cycle's size [15] and formation of bicyclic pyrrolidine derivatives.

The obtained unsaturated amino alcohol **5** was subjected to the aza-Cope–Mannich reaction with a series of aldehydes, affording the corresponding tricyclic structures. In almost all cases the reaction proceeded stereoselectively, and we observed the formation of only one pair of diastereomers (according to 2D NMR and X-ray data [15]) in high yield (above 70%). In only one case (compound **10**), a mixture of two diastereomeric products was obtained, also in high combined yield (above 70%). These isomeric mixtures were successfully separated by column chromatography. Analysis of the stereochemistry of the transition states allowed us, in some instances, to predict the conditions under which preferential formation of the desired isomer occurred. It is important to note that decreasing the size of the aldehyde (t Bu or Ph → Me) reduces the steric repulsion between the methyl group and R, leading to the formation of a mixture of (E)- and (Z)-iminium ions and, consequently, a mixture of diastereomers. DCM was used as the solvent for all synthetic transformation to obtain the desired tricycles.



Scheme 3

For tricycle **8**, we were able to determine the relative configuration of the stereocenters [15]. It should be noted that the starting unsaturated amino alcohol **5** was used as a racemic mixture. Thus, if this mixture is resolved into individual enantiomers or an enantioselective synthesis of this alcohol is achieved, it can be anticipated that the key transformation would yield a single stereoisomer.

The construction of this tricyclic platform—tetralone derivatives—opens up a wide range of possibilities for molecular modification. By varying the substituent on the aldehyde, the substituent at the C2 position can be altered. Using different bromoalkenes in the synthesis allows the modification of substituents at the C3 and C3a positions. The presence of the carbonyl group in the tricycle also provides ample opportunities for straightforward chemical modifications of this unique tricyclic system.

Notably, the transformation is insensitive to the order of reagent addition, requires no inert atmosphere, and proceeds at ambient temperature or with gentle heating. Moreover, the reaction exhibits excellent scalability, allowing for the acquisition of tricyclic products in sufficient amounts for subsequent synthetic investigations and biological assays [7].

In the initial phase of the experiment, we evaluated the cytotoxicity of the test substances on two cell lines: Vero cells, which are used as host cells for herpes simplex virus type 1, and MRC-5 cells, which serve as host cells for cytomegalovirus. The findings from the cytotoxicity tests are summarized in Table 2.

Table 2 Results of cytotoxicity assessment of the tested substances on Vero and MRC-5 cell cultures.

Compound	CC_{50}, μg/mL	
	Vero	MRC-5
6	294.2	119
7	473.4	106.8
8	251.7	83.7
9	262.4	114.9

The data show that the test substances exhibit low-to-moderate cytotoxicity on both cell lines.

In the next step, the compounds were tested to assess their antiviral activity; the results are presented in Table 3.

Table 3 Results of antiviral activity assessment of the tested against cytomegalovirus and herpes simplex virus

Compound	CMV		HSV-1	
	IC_{50}, μg/ml	SI	IC_{50}, μg/ml	SI
6	22.95±5.6	5.19	>294.2	1
7	45.7±8.9	2.34	>473.4	1
8	165.5±12.8	0.51	>251.7	1
9	22.67±3.4	5.07	>262.4	1

A series of saturated heterocyclic compounds with annulated rings were synthesized using the aza-Cope–Mannich rearrangement as the key transformation step and evaluated for their antiviral activity against herpes simplex virus (HSV) and cytomegalovirus (CMV), as well as for their cytotoxicity in Vero and MRC-5 cell cultures. Two of these compounds demonstrated moderate inhibitory activity against CMV, with IC_{50} values of approximately 23 μg/mL and selectivity indices (SI) around 5. Although the current selectivity indices are below the threshold typically considered promising for drug candidates (SI > 8), these results identify the tricyclic cis-fused pyrrolidine core as a candidate chemotype with anti-CMV activity worth further investigation. This study provides the first synthetic access to this tricyclic system, highlights the anti-CMV potential of this scaffold, and establishes a foundation for further structural optimization in future medicinal chemistry efforts.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:

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