Synthesis of Cyclohepta[b]indoles by (4 + 3) Cycloaddition of 2-Vinylindoles or 4H-Furo[3,2-b]indoles with Oxyallyl Cations

Valentina Pirovano,* Elisa Brambilla, Andrea Moretti, Silvia Rizzato, Giorgio Abbiati, Donatella Nava, and Elisabetta Rossi*

ABSTRACT: The synthesis of cyclohepta[b]indole derivatives through the dearomative (4 + 3) cycloaddition reaction of 2-vinylindoles or 4H-furo[3,2-b]indoles with in situ generated oxyallyl cations is reported. Oxyallyl cations are generated from α-bromoketones in the presence of a base and a perfluorinated solvent. Cyclohepta[b]indole scaffolds are obtained under mild reaction conditions, in the absence of expensive catalysts, starting from simple reagents, in good to excellent yields and with complete diastereoselectivity. Preliminary expansion of the scope to 3-vinylindoles and to aza-oxyallyl cations is reported.

INTRODUCTION

The cyclohepta[b]indole is the core privileged structure of a variety of natural as well as non-natural compounds having different degrees of structural complexity in addition to a great variety of biological activities. Gaich and Stempel have recently organized all of these features in an exhaustive review. In particular, they describe the structural geography of different families of cyclohepta[b]indoles alkaloids ranging from the simplest exotines and ervitsine−ervatamine alkaloids to the more complex actinophyllic acid and ambiguines (Figure 1).

Moreover, as is often the case, the reported biological activities attracted the interest of both medicinal and synthetic chemists for the rational design of new therapeutic agents (Figure 2) and for the development of efficient synthetic methods.

Figure 1. Natural products containing the cyclohepta[b]indoles scaffold.

Figure 2. Non-natural cyclohepta[b]indole derivatives.

It is about this last aspect that Gaich and Stempel have made several useful points. Notably, apart from the well-known Fischer indole synthesis, limited to the synthesis of symmetrically substituted cyclohepta[b]indoles, most reported methodologies involve the use of cycloaddition reactions, sigmatropic rearrangements, and palladium-catalyzed cyclizations. The most representative and versatile protocols involve (4 + 3) cycloadditions (Scheme 1) and were developed,
beyond the examples reported by Gaich and Stempel, also in their enantioselective version.\textsuperscript{7}

**Scheme 1. Indolyl Derivatives as 3C Partners in (4 + 3) Cycloadditions with Dienes\textsuperscript{4}\textsuperscript{a}**

In these cycloaddition reactions, the indolyl moiety functions as the 3C partner, whereas (4 + 3) cycloaddition reactions having indoles as the 4C component have become operative only more recently (Scheme 2).\textsuperscript{8}

**Scheme 2. Previous and Present Works Using Indoles as 4C Components\textsuperscript{4}\textsuperscript{a}**

For example, in 2017, Zhang and co-workers reported a regioselective gold-catalyzed (4 + 3) cascade cycloaddition/CH functionalization of 2-vinylindoles and propargylic esters leading to highly substituted derivatives.\textsuperscript{9} In 2018, Sun described an enantioselective rhodium-catalyzed (4 + 3) cycloaddition of both 2- and 3-vinylindoles with vinyl-diazoesters leading to dearomatized cyclohepta[\(b\)]indolines in high yields and enantiomeric excesses.\textsuperscript{8b} A 3-alkenylindole was also considered as the reactive intermediate in the iron(III)-catalyzed reaction between simple indoles and o-hydroxychloraldehyde.\textsuperscript{10} Taking into account these precedents and our interest in the synthesis of complex indole derivatives through cycloaddition reactions of 2-vinylindoles,\textsuperscript{9} we decided to test the reactivity of 2-vinylindoles with oxallyl cations in order to synthesize cyclohepta[\(b\)]indoles through (4 + 3) cycloaddition reactions. The use of oxallyl cations as three-carbon partners in [3 + n] cycloadditions has been widely studied and includes both (3 + 2)\textsuperscript{10} and (4 + 3)\textsuperscript{11} cycloaddition reactions. Oxallyl cations can be generated from \(\alpha\)-haloketones, \(\alpha,\alpha\prime\)-dihalo-\(\alpha\)-ketones, and allen oxides and by Nazarov cyclization,\textsuperscript{12} among other precursors. We chose to focus our attention on the base-mediated dehydrohalogenation of \(\alpha\)-haloketones. This approach, in fact, employs simple and easy-accessible starting materials allowing for the easy generation of diversely substituted oxallyl cations. In this paper, we report a full account of the obtained results.

**RESULTS AND DISCUSSION**

In order to test the viability of our idea, 2-vinylindole 1\(a\) and 2-bromocyclopentan-1-one 2\(a\) were selected as model substrates and reacted in the presence of different bases and/or fluorinated solvents. These solvents, in fact, possess unique qualities, including the capability to activate carbonyl groups and stabilize cationic intermediates, and were reported as solvents of choice in related reactions.\textsuperscript{13} The results obtained during the optimization of the reaction conditions are summarized in Table 1.

At the outset, we focused our attention on the influence of different bases on the reaction outcome using 2,2,2-trifluoroethanol (TFE) as the solvent. Both inorganic (Na\(_2\)CO\(_3\), entry 1) and organic bases, [Et\(_3\)N, N,N-diisopropyl-llethylamine (DIPEA), and 1,8-diazabicycloundec-7-ene (DBU), entries 2–4], led to the formation of desired deearomatized cycloadduct 3\(a\) together with a minor amount of product 4\(a\) arising from the nucleophilic addition of C3 of the indole nucleus on the in situ generated oxallyl cation.\textsuperscript{14} Better results in terms of the 3\(a\)/4\(a\) ratio were achieved with DIPEA, which was selected as the best base for the following optimization steps. Then, in order to reduce the competitive formation of 4\(a\), we modified both the reaction temperature and solvent. However, the reduction of the reaction temperature down to \(-20\) °C (entry 5), as well as the use of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) (entry 6), had a negative impact on the formation of 3\(a\), increasing the formation of 4\(a\). Taking into account these results, we decided to verify the influence of TFE in promoting the formation of the desired cycloadduct 3\(a\), by a progressive increase of its concentration from 1 to 6 equiv in a 0.5 M solution of the reactants in toluene. As a result, we observed that the use of an equimolar amount of TFE (entry 7) significantly reduced the reaction rate but strongly inhibited the formation of 4\(a\). A better yield and faster reaction time were obtained using 3 equiv of TFE (entry 8). The optimal 88% yield of 3\(a\) was finally achieved employing 6 equiv of fluorinated alcohol (entry 9).

Switching from toluene to dichloromethane slightly worsened the reaction outcome in both terms of yield and selectivity (entry 10), while the use of a classical Lewis acid such as LiClO\(_4\) in diethyl ether led to a significantly lower yield (entry 11).\textsuperscript{11} Notably, in all tested reactions, 3\(a\) was isolated as a single diastereoisomer, the structure of which was fully
Table 1. Optimization of Reaction Conditions for the Synthesis of 3a\(^{1-3}\)

| entry | base | solvent | time, h | 3a (%) | 4a (%) |
|-------|------|---------|---------|--------|--------|
| 1     | Na\(_2\)CO\(_3\) | TFE (1 M) | 3       | 67     | 17     |
| 2     | Et\(_3\)N | TFE (1 M) | 1       | 56     | 26     |
| 3     | DIPEA | TFE (1 M) | 1       | 75     | 17     |
| 4     | DBU | TFE (1 M) | 3       | 50     | 15     |
| 5\(^{a}\) | DIPEA | HFIP (1 M) | 2       | 53     | 47     |
| 6     | DIPEA | HFIP (1 M) | 1       | 53     | 47     |
| 7     | DIPEA | TFE (1 equiv) toluene (0.5 M) | 22      | 32     | <5     |
| 8     | DIPEA | TFE (3 equiv) toluene (0.5 M) | 6       | 53     | <5     |
| 9     | DIPEA | TFE (6 equiv) toluene (0.5 M) | 1       | 88     | <5     |
| 10    | DIPEA | TFE (6 equiv) CH\(_2\)Cl\(_2\) (0.5 M) | 1       | 74     | 13     |
| 11    | DIPEA | LiClO\(_4\) (1 equiv) Et\(_2\)O (0.5 M) | 22      | 27     | <5     |

\(^{a}\)Reaction conditions: 1a (0.2 mmol), 2a (0.28 mmol), base (0.3 mmol) in the stated solvent or in TFE/solvent mixture at rt for 1–22 h. \(^{b}\)Isolated yield. \(^{c}\)Reaction performed at \(-20^\circ C\).

Elucidated by 1D- and 2D-NMR analyses (see Supporting Information).

With the best conditions in hand, we then explored the scope of the reaction with different substituted 2-vinylindoles and \(\alpha\)-bromoketones (Scheme 3).

We first focused on the modification of the indole vinyl moiety by using different \(\beta\)-alkyl and \(\beta\)-aryl-substituted 2-vinylindoles. The substitution of the methyl group with a longer alkyl chain or with a cyclohexyl ring was well tolerated, and the corresponding indolines \(3b\) and \(3c\) were isolated in 58 and 69% yield, respectively, in addition to residual amounts of starting vinylindoles, nucleophilic substitution products (less than 10%), and traces of other unidentified side products. Aryl-substituted 2-vinylindoles reacted efficiently as well. In particular, 4-methylystyrylvinyllinolide (1d) afforded 3d in a satisfying 80% yield, while related vinylindoles bearing electron-withdrawing (1e) or electron-donating (1f) substituents led to cycloadducts 3e–f in comparable 70 and 79% yields. Next, we introduced different substituents at S-position of the indole skeleton in order to evaluate variation in the reactivity of the vinylindole due to a reduced or augmented nucleophilicity of the carbon in position 3. As a result, we observed that 5-fluoro derivative 1g smoothly reacted with 2a to give 3g in 68% yield, while 5-methoxy-substituted 1h led to 3h in 70% yield. We then evaluated the influence of ketones other than 2-bromocyclopentan-1-one on the reaction course. The employment of 2-bromo-2-methylcyclopentan-1-one (2b) was tolerated; however, the reaction performed under optimized conditions resulted in a significantly lower conversion of starting materials even after prolonged reaction times (less than 10% after 96 h at rt). Surprisingly, with this more substituted ketone, the use of TFE as the sole solvent (1 M) permitted the isolation of 3i in a satisfying 72% yield. Similarly, symmetrically substituted acyclic ketones 2c and 2d led to the corresponding products 3j and 3k in 78 and 55% yields, respectively, only when TFE was used as the solvent. In all the last cases, a residual amount of unreacted vinylindole was recovered along with traces of unidentified byproducts. On the other hand, the reaction between 1a and non-symmetrically substituted ketone 2e was more challenging and did not proceed even in TFE at 40 °C. In this case, after a brief screening of reactions conditions, we were able to isolate 3l as a single isomer in moderate 37% yield, only by using Na\(_2\)CO\(_3\) (0.3 mmol) as a base in TFE (1 M) for 48 h at 40 °C.

Scheme 3. Scope of the Reaction between 1a–h and 2a–e\(^{a}\)

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| 3a R1 = Mo, R2 = H, 68% |
| 3b R1 = N+PF6, R2 = H, 58% |
| 3c R1 = CO2Et, R2 = H, 69% |
| 3d R1 = 4-Me-C6H4-C6H4, R2 = H, 80% |
| 3e R1 = 3,3′-CH2-C6H4, R2 = H, 70% |
| 3f R1 = 4,4′-CH2-C6H4, R2 = H, 79% |
| 3g R1 = 4,4′-CH2-C6H4, R2 = F, 68% |
| 3h R1 = 4,4′-CH2-C6H4, R2 = OH, 70% |
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\(^{a}\)Reaction conditions: 1a–h (0.2 mmol), 2a–e (0.28 mmol), DIPEA (0.3 mmol), and TFE (1.2 mmol) in toluene (0.4 mL) for 1 h at rt. TFE (1 M) was used as the solvent for 24 h at rt. Na\(_2\)CO\(_3\) (0.3 mmol) was used as a base in TFE (1 M) for 48 h at 40 °C.

Scheme 4. Reaction between 1j–l and 2a

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+ R = Boc, 3m: 72%
+ R = Me, 3a: 72%
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Moreover, in the context of our studies on the metal-catalyzed functionalization of indoles, we recently reported the synthesis of ethyl 4H-furo[3,2-b]indole-4-carboxylates, an interesting class of heterocyclic compounds, which could be employed in gold-catalyzed reactions to give indolin-3-one derivatives. Taking a look into the structure of these substrates, we observed that they could be considered as an attractive alternative to 2-vinylindoles, in which the diene system is embedded in the furan ring and constrained in a s-cis conformation. Thus, we decided to test their reactivity in these (4 + 3) cycloadditions under the previously optimized conditions in order to expand the scope of our transformation (Scheme 5).

As supposed, when we reacted 4H-furo[3,2-b]indole-4-carboxylate 5a with cyclopentyl oxyallyl cation generated in situ with TFE and DIPEA, we were able to isolate 7,8-dihydro-5H-7,10a-epoxycyclohepta[b]indole derivative 6a as a single product in high yields (77%) after 2 h. Notably, in this case, no product arising from the nucleophilic substitution on the furan moiety was observed or isolated. As for 3a, the structure of indoline 6a was confirmed by 2D-NMR spectra and by X-ray diffraction analysis on a single crystal (see Supporting Information for details).

Similarly, 3-substituted furindoles 5b–d were efficiently transformed into their corresponding cycloaddition products 6b–d, suggesting that the presence of both electron-withdrawing and electron-donating groups on the furan moiety does not affect the reaction outcome. We also employed furindoles substituted on the furan moiety. In this case, methyl-substituted 5e afforded 6e in 77% yield after 3 h. Finally, as for 2-vinylindoles, 2-bromopentan-3-one (2c) and 1-bromo-1,3-diphenylpropan-2-one (2d) were used instead of 2a. The reaction of these haloketones required the use of TFE as the solvent and resulted in the isolation of 6f and 6g in 78 and 95% yield, respectively. In addition, 1-bromo-3-methylbutan-2-one (2e) reacted with 5a to give 6h as a single isomer in 57% yield, but only when Na2CO3 was used as a base in TFE at 40 °C for 48 h.

Further, considering the great number of reports on cycloaddition reactions with aza-oxyallyl cations, we decided to examine whether these substrates could be suitable partners in the (4 + 3) cycloaddition with vinylindole 1a under our optimized conditions (Scheme 6). However, in this case, the reactions were extremely slow, and only traces of products were observed after 24 h. Using pure TFE as the solvent, we were able to isolate a 14% yield of 8 after 24 h, while the switch to other fluorinated alcohols such as HFIP led to rapid and full conversion of the starting material to give a separable 1:1 mixture of (4 + 3) and (3 + 2) cycloaddition products, 8 and 9, in overall 82% yield. Further studies to improve the selectivity toward (4 + 3) cycloadducts are now in progress in our laboratory. In addition, we tested the reactivity of furindole 5a, and in this case, we were able to isolate cycloadduct 10 as a single product in 63% yield.

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Subsequently, we studied the behavior of 3-vinylindoles by reacting 11 and 2a under the optimized conditions. Substrate 11 was less reactive than the isomeric 2-vinylindole 3d, and the reaction required 24 h to afford cycloadduct 12 in 67% yield (Scheme 7). In addition, the same substrate reacted with azaoxyallyl cation generated from 7 to give (4 + 3) derivative 13.
13 as a single product using HFIP as the solvent. In this case, the reaction was also slow and required 24 h to provide 13, in addition to unreacted 3-vinylindole.

Having synthesized a series of cyclohepta[b]indoles 3a–l, we finally focused our attention in proposing simple and effective modifications of these scaffolds. To this end, 3d was prepared on a gram scale, and it was subjected to selected transformations (Scheme 8). Thus, we observed that 3d quantitatively aromatized to give 14 upon treatment with catalytic amounts of p-TsOH, while under basic hydrolytic conditions, NH-free aromatic cycloheptaindole 15 was isolated in 78% yield. Moreover, the cycloheptanone ring of 3d was effectively and selectively reduced with sodium borohydride to give the corresponding alcohol 16 in 65% yield.

As above mentioned, aromatization of 3d easily occurred under acid conditions affording the corresponding product almost quantitatively. For this reason, we became interested in verifying the behavior of 6a under the same reaction conditions, considering that aromatization of such a product would probably require the ring-opening of the epoxy ring. Nevertheless, when we treated 6a with catalytic amounts of p-TsOH in chloroform, we isolated the sole 2-(2-oxocyclopentyl)-4H-furo[3,2-b]indole derivative 17 in high 94% yield (Scheme 9). This result was not unexpected, and a similar behavior has already been described by Harmata for the acidic treatment of cycloadducts synthesized starting from 2-chlorocyclopanones and furans.20 Additionally, the conversion of 6a to substituted furan 17 could be mechanistically ascribed to a Grob fragmentation21 of protonated 6a, followed by the regeneration of the furan moiety and keto–enol tautomerism to regenerate the cyclopentanone ring (Scheme 9).

A plausible reaction mechanism for the (4 + 3)-cycloaddition reactions is not easy to describe nor to predict. In general, the reaction can be viewed as a (4 + 3) cycloaddition that relies on the use of α-halo ketones as oxyallyl cation precursors (C3 fragment) and 2-vinylindoles or furinoindoles as dienes (C4 fragment). Moreover, based on the IUPAC convention, the process is a homologue of the Diels–Alder reaction, a standard [4 + 2] cycloaddition considering the numbers of electrons involved. As reported in the literature,14b,c,d these reactions occur through pathways ranging from a classical pure concerted process to processes that are stepwise (Scheme 10).

The nature of the substrates involved as well as the reaction conditions employed affect the mechanism and in turn the chemical and stereoselective outcome of the reaction. In our cycloadditions, we observed complete regio- and diastereoselectivity. The stereochemistry of the isolated compounds arose from an endo approach between the diene and the dienophile (Figure 3).

Both open chain internal–external ring dienes (vinylindoles) and dienes embedded in a furan ring (furoindoles) gave analogous results. The same occurred using both cyclic and acyclic oxyallyl cation precursors. Based on these results, our reactions could be viewed as proceeding via a concerted mechanism. However, looking at the electronic features of the reacting dienes (polarized, electron rich) and dienophiles (electrophilic, TFE-stabilized), a pseudconcerted or fast stepwise process cannot be excluded. In this context, Cramer and co-workers recently reported the results of their computational studies on the mechanism of related reactions.

**Scheme 8. Selective Functional Group Transformations on Product 3d**

**Scheme 9. Behavior of 6a under Acid Conditions**

**Scheme 10. (a) Plausible Reaction Mechanism for (4 + 3) Cycloaddition with Oxyallyl Cations; (b) Formation of Nucleophilic Substitution Compound 4**

**Figure 3. Stereochemical outcome derived from the endo approach.**
particular, they demonstrated that stepwise processes are more favored for electron-rich dienes and electrophilic oxayllyl cations. Furthermore, a mechanism involving catonic intermediates is plausibly operating in the reaction of 2-vinylindoles as demonstrated by the isolation of compound 4a, arising from the first intermediate of the stepwise process by a proton elimination/re-aromatization reaction (Scheme 10).

Finally, several remarks on the role of TFE on the reaction outcome can be made. The role of TFE in these reactions is to assist and accelerate the deprotonation of α-haloketones and their subsequent ionization, via hydrogen bond formation. Cyclic ketones require low amounts of TFE probably because they are sufficiently reactive to participate in the cycloaddition. Indeed, an excess of TFE lowers the reaction selectivity, favoring the formation of undesired nucleophilic substitution compounds. However, when open chain and hindered substrates were involved, pure TFE must be used as the solvent, in some cases in the presence of a base stronger than DIPEA in order to facilitate both the enolation and the abstraction steps.

### CONCLUSIONS

In conclusion, we developed a selective and efficient synthesis of complex cyclohepta[b]indole derivatives through the dearomatized (4 + 3) cycloaddition reaction of vinylindoles or 4H-furo[3,2-b]indoles with oxayllyl cations. Oxayllyl cations are efficiently generated in situ starting from the corresponding α-haloketones using DIPEA and TFE under mild reaction conditions.

Differently from the well-known methods for synthesizing cyclohepta[b]indole, in which the indolyl moiety contributes to the (4 + 3) cycloaddition as a 3C unit, our approach exploits the ability of vinylindoles to react as a 4C partner in these cycloaddition reactions. It is worth noting that the use of these latter substrates in (4 + 3) cycloaddition reactions has been scarcely described in the literature. Moreover, the existing methodologies require the intermediary of a metal vinylcarbene intermediate as a 3C partner, generated from propargyl esters or vinylidiazooacetates under gold and rhodium catalysis. Thus, the results obtained herein represent an expansion of the reactivity of vinylindoles as a 4C partner with C3 counterparts such as oxayllyl cations and demonstrate their utility as building blocks to create complex molecular architectures. Finally, a clear advantage resides in the use of simple and inexpensive starting materials, solvents, and additives that do not require the use of strictly controlled reaction conditions. The extension of the scope to other substrates such as 3-vinylindoles and 2a-oxayllyl cations was also briefly explored as were further transformations of the obtained products.

### EXPERIMENTAL SECTION

All chemicals and solvents are commercially available and were used after distillation or treatment with drying agents. Silica gel F254 thin-layer plates were employed for thin-layer chromatography. Silica gel 40–63 μm/60 Å was employed for flash column chromatography. Melting points were measured with a PerkinsElmer DSC 6 calorimeter at a heating rate of 5 °C/min and are uncorrected. 1H and 13C NMR spectra were determined with a Varian-Gemini 300, a Bruker 300, 500 AVANCE or 600 Bruker spectrometers at room temperature in CDCl3, CD2Cl2, CD3OD, or aceton-d6 with residual solvent peaks as the internal reference. The APT sequences were used to distinguish the methine and methyl carbon signals from those arising from methylene and quaternary carbon atoms. Two-dimensional NMR experiments were performed for products 3a, 3d, 3i, 3j, 3l, 6a, 6f, 6h, 8, 9, 10, 12, 16, and 17 to aid the assignment of structures. Low-resolution mass spectrometry (MS) spectra were recorded with a Thermo-Finnigan LCQ Advantage AP electrospray/ion trap equipped instrument using a syringe pump device to directly inject sample solutions.

2-Vinylindoles 1a–m,21 ethyl 4H-furo[3,2-b]indole-4-carboxylates 5a–e,22 ethyl (E)-3-[(4-methylstyryl)-1H-indole-1-carboxylate 11,24 α-haloketones 2a–e,25 and N-([benzoxyl]-2-bromo-2-methylpropiynamide 719 are known compounds and were prepared according to literature procedures.

**General Procedure for the Reaction between 2-Vinylindoles 1a–i and α-Haloketones 2a–e.** To a stirring solution of 2-vinylindole 1a–i (0.2 mmol, 1.0 equiv), α-haloketone 2a–e (0.28 mmol, 1.4 equiv), and TFE (86.4 μL, 1.2 mmol, 60 equiv) in toluene (0.4 mL, 0.5 M), DIPEA (52.3 μL, 0.3 mmol, 1.5 equiv) was added, and the mixture was stirred for 1 h at room temperature. The solvent was then removed, and the crude was purified by column chromatography to yield the corresponding cyclohepta[b]indole 3a–m.

Ethyl 7-Methyl-12-oxo-7,8,9,10,11,11a-hexahydro-5H-8,11-methanocycloocta[b]indole-5-carboxylate (3a). The general procedure was followed using ethyl (E)-2-(prop-1-en-1-yl)-1H-indole-1-carboxylate 1a (46.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one 2a (46.0 mg, 0.28 mmol). The purification of the crude by flash chromatography (SiO2, hexane/ethyl acetate 95:5) yielded 3a (55 mg, 88%) as a yellow thick wax.

**Ethyl 12-Oxo-7-propyl-7,8,9,10,11,11a-hexahydro-5H-8,11-methanocycloocta[b]indole-5-carboxylate (3b).** The general procedure was followed using ethyl (E)-2-(pent-1-en-1-yl)-1H-indole-1-carboxylate 1b (51.5 mg, 0.2 mmol) and 2-bromocyclopentan-1-one 2a (46.0 mg, 0.28 mmol). The purification of the crude by flash chromatography (SiO2, hexane/ethyl acetate 95:5) yielded 3b (39 mg, 58%) as a yellow thick wax.

**Ethyl 12-Oxo-7-cyclohexyl-12-oxo-7,8,9,10,11,11a-hexahydro-5H-8,11-methanocycloocta[b]indole-5-carboxylate (3c).** The general procedure was followed using ethyl (E)-2-(2-cyclohexenyl)-1H-indole-1-carboxylate 1c (59.5 mg, 0.2 mmol) and 2-bromocyclopentan-1-one 2a (46.0 mg, 0.28 mmol). The purification of the crude by flash chromatography (SiO2, hexane/ethyl acetate 95:5) yielded 3c (52 mg, 69%) as a white thick wax.
30.2 (CH2), 26.6 (CH2), 26.5 (CH2), 26.4 (CH2), 22.3 (CH3), 21.3 (CH3), 13.9 (CH3). ESI(+)-MS m/z (%): 380 (100) [M + H]+. Anal. Calc. for C26H27NO4: C, 74.80; H, 6.52; N, 3.34.

**Ethyl 7-(4-Fluorophenyl)-12-oxo-7,8,9,10,11,11a-hexahydro-5H,8,11-methanocycloocta[b]indole-5-carboxylate (3e).** The general procedure was followed using ethyl 2-(4-methylstyryl)-1H-indole-1-carboxylate (62.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one (46.0 mg, 0.28 mmol). The purification of the crude by flash chromatography (SiO2, hexane/ethyl acetate 9:1) yielded 3e (54 mg, 70% yield). ESI(+)-MS m/z (%): 392 (100) [M + H]+. Anal. Calc. for C24H25NO3: C, 77.62; H, 6.76; N, 3.50.

**Ethyl 7-(4-Methoxyphenyl)-12-oxo-7,8,9,10,11,11a-hexahydro-5H,8,11-methanocycloocta[b]indole-5-carboxylate (3f).** The general procedure was followed using ethyl 2-(4-methoxystyryl)-1H-indole-1-carboxylate (64.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one (46.0 mg, 0.28 mmol). The purification of the crude by column chromatography (SiO2, hexane/ethyl acetate 9:1) yielded 3f (49.5 mg, 28% yield). ESI(+)-MS m/z (%): 404 (100) [M + H]+. Anal. Calc. for C24H25NO3: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.62; H, 6.76; N, 3.50.

**Ethyl 7,8,10-Trimethyl-9-oxo-8,9,10,10a-tetrahydrocyclohepta[b]indole-5-(7H)-carboxylate (3i).** The general procedure was followed using ethyl 2-(4-methoxystyryl)-1H-indole-1-carboxylate (61.0 mg, 0.22 mmol) and 2-bromomethylcyclopentan-1-one (46.0 mg, 0.28 mmol). The purification of the crude by column chromatography (SiO2, hexane/ethyl acetate 9:1) yielded 3i (58 mg, 72% yield) as a yellow thick wax. ESI(+)-MS m/z (%): 402 (100) [M + H]+. Anal. Calc. for C23H24NO3: C, 76.44; H, 6.57; N, 3.39. Found: C, 76.41; H, 6.57; N, 3.39.

**Ethyl 7,10-Trimethyl-9-oxo-8,9,10,10a-tetrahydrocyclohepta[b]indole-5-(7H)-carboxylate (3j).** The general procedure was followed using ethyl 2-(prop-1-en-1-yl)-1H-indole-1-carboxylate (64.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one (46.0 mg, 0.28 mmol). The purification of the crude by column chromatography (SiO2, hexane/ethyl acetate 9:1) yielded 3j (67.0 mg, 0.22 mmol) and 2-bromomethylcyclopentan-1-one (60 mg, 0.2 mmol). The purification of the crude by flash chromatography (SiO2, hexane/ethyl acetate 4:1) yielded 3j (58 mg, 72%). ESI(+)-MS m/z (%): 400 (100) [M + H]+. Anal. Calc. for C23H24NO3: C, 76.43; H, 6.57; N, 3.39. Found: C, 76.42; H, 6.57; N, 3.48.
**Ethyl 7-Methyl-9-oxo-8,10-diphenyl-8,9,10,10a-tetrahydrocyclohepta[b]indole-5(7H)-carboxylate (3k).** The general procedure was followed using ethyl (E)-2-(prop-1-en-1-yl)-1H-indole-1-carboxylate 1a (460 mg, 0.2 mmol) and 1-chloro-1,3-diphenylprop-2-one 2d (63.0 mg, 0.28 mmol) for 24 h at rt. TFE (0.2 mL, 1 M) was used as the solvent instead of toluene. The purification of the crude by column chromatography (SiO$_2$, hexane/ethyl acetate 95:5) yielded 3k (48 mg 55%) as a yellow thick wax. 1H NMR (300 MHz, CD$_2$Cl$_2$): 7.99 (d, J = 8.3 Hz, 1H), 7.09–6.97 (m, 6H), 6.93–6.82 (m, 5H), 6.68 (dd, J = 5.8, 2.4 Hz, 1H), 6.55 (td, J = 7.5, 1.0 Hz, 1H), 6.46 (dd, J = 6.9, 0.7 Hz, 1H), 4.74 (dd, J = 11.2, 1.0 Hz, 1H), 4.05 (q, J = 7.1 Hz, 2H), 3.80 (d, J = 11.0 Hz, 1H), 3.69 (d, J = 11.3 Hz, 1H), 3.16 (m, 1H), 1.06–0.91 (m, 6H), 1H). Anal. Calcd for C$_{31}$H$_{26}$NO$_3$: C, 75.24; H, 5.21; N, 4.00. Found: C, 75.07; H, 4.98; N, 3.92.

**Preparation and Characterization Data for Compounds 4a–b.** *Ethyl (E)-3,2-Oxycyclopropyl-2-(prop-1-en-1-yl)-1H-indole-1-carboxylate (4a).* 4a was isolated during the screening of reaction conditions (see Table 1) as a secondary product by reacting ethyl (E)-2-(prop-1-en-1-yl)-1H-indole-1-carboxylate 1a (460 mg, 0.2 mmol) and 2-bromocyclopentan-1-one 2a (46 mg, 0.28 mmol) for 24 h at 40 °C. The general procedure was followed using ethyl (E)-2-(pent-1-en-1-yl)-1H-indole-1-carboxylate 1b (67 mg, 0.3 mmol) as a yellow solid (mp 149 – 150 °C). Anal. Calcd for C$_{21}$H$_{25}$NO$_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.57; H, 7.42; N, 4.13.

**General Procedure for the Reaction between 4H-Furo[3,2-b]indole 5a–e and α-haloketones 2a–c.** To a stirring solution of 4H-furo[3,2-b]indole 5a–e (0.2 mmol, 1.0 equiv) and α-haloketone 2a–c (0.28 mmol, 1.4 equiv), and TFE (86.4 mL, 1.0 mmol, 6.0 equiv) in toluene (0.4 mL, 0.5 M), DIPEA (52.3 µL, 0.3 mmol, 1.5 equiv) was added, and the mixture was stirred for 2–3 h at room temperature. The Solvent was then removed, and the crude was purified by column chromatography to yield the corresponding cyclohepta[5]indoline 6a–h.

**Ethyl 13-Oxo-8,9,10,11-tetrahydro-7,11a-epoxy-8,11-methanocycloocta[b]indole-5(7H)-carboxylate (6a).** The general procedure was followed using ethyl 4H-furo[3,2-b]indole 4a-carboxylate 5a (46.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one 2a (46.0 mg, 0.28 mmol) for 3 h at rt. The purification of the crude by flash chromatography (SiO$_2$, hexane/ethyl acetate 95:5) yielded 6a (48 mg 77%) as a yellow solid (mp 116–118 °C). 1H NMR (300 MHz, CDCl$_3$): 7.98 (d, J = 6.4 Hz, 1H), 7.48 (m, 1H), 7.41 (td, J = 8.2, 1.2 Hz, 1H), 7.14 (td, J = 7.5, 0.6 Hz, 1H), 5.81 (s, 1H), 4.99 (dd, J = 4.2, 2.2 Hz, 1H), 4.40 (m, 2H), 2.67 (m, 1H), 2.42–2.27 (m, 2H), 2.15 (m, 1H), 1.98–1.87 (m, 2H), 1.41 (J, J = 7.1, 3.0 Hz). Anal. Calcd for C$_{29}$H$_{27}$NO$_3$: C, 79.61; H, 7.42; N, 4.13. Found: C, 79.57; H, 7.42; N, 4.13.

**Ethyl 2-Fluoro-13-Oxo-8,9,10,11-tetrahydro-7,11a-epoxy-8,11-methanocycloocta[b]indole-5(7H)-carboxylate (6b).** The general procedure was followed using ethyl 7-fluoro-4H-furo[3,2-b]indole 5b (50.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one 1a (46.0 mg, 0.28 mmol) for 2 h at rt. The purification of the crude by flash chromatography (SiO$_2$, hexane/ethyl acetate 95:5) yielded 6b (46 mg 70%) as a yellow solid (mp 136–140 °C). 1H NMR (300 MHz, CDCl$_3$): 7.99 (br s, 1H), 6.88 (dd, J = 7.5, 2.7 Hz, 1H), 6.66 (id, J = 9.0, 2.8 Hz, 1H), 5.45 (br s, 1H), 4.33 (dd, J = 4.3, 2.2 Hz, 1H), 3.81 (m, 2H), 2.19 (m, 1H), 2.04 (m, 1H), 1.80 (m, 1H), 1.65 (m, 1H), 1.50–1.33 (m, 2H), 0.79 (s, J = 7.1 Hz, 1H). Anal. Calcd for C$_{29}$H$_{27}$NO$_3$: C, 79.61; H, 7.42; N, 4.13. Found: C, 79.57; H, 7.42; N, 4.13.
Ethyl 2-Methyl-13-oxo-8,9,10,11-tetrahydro-7,11a-epoxy-8,11-methanocycloocta[blindle-5(7H)-carboxylate (6c). The general procedure was followed using ethyl 7-methyl-4H-furo[3,2-b]-indole-4-carboxylate (5c (40.0 g, 0.2 mmol) and 2-bromocyclopentanone-1-one 2a (460 mg, 0.28 mmol) for 2 h at rt. The purification of the crude by flash chromatography (SiO2, hexane/ethyl acetate 95:5 to 9:1) yielded 6e (52 mg, 80%) as an orange solid (mp 114–117 °C). H NMR (300 MHz, CDCl3): 8.16 (br s, 1H), 7.07 (m, 1H), 6.85 (m, 1H), 5.53 (br s, 1H), 4.42 (dd, J = 4.2, 2.2 Hz, 1H), 3.84 (m, 2H), 2.31–2.13 (m, 2H), 2.04 (m, 1H), 1.93 (s, 3H), 1.75 (m, 1H), 1.54–1.34 (m, 2H), 0.81 (s, 1H, J = 7.1 Hz, 3H).

13C{1H} NMR (75 MHz, CDCl3): 205.5 (C), 150.98 (C), 143.5 (C), 133.4 (C), 130.7 (CH), 129.1 (C), 126.7 (C), 123.9 (CH), 116.0 (CH), 106.9 (CH), 91.8 (C), 87.0 (CH), 62.2 (CH2), 56.5 (CH2), 50.7 (CH), 22.3 (CH2), 21.0 (CH2), 20.4 (CH3), 13.7 (CH3). ESI(+-)MS m/z (%): 326 (100) [M + H]+. Anal. Calcd for C24H23NO2C: 70.14; H, 5.89; N, 4.31. Found: C, 69.92; H, 5.90; N, 4.29.

Ethyl 2-Methoxy-8-oxo-9,10,11-tetrahydro-7,11a-epoxy-8,11-methanocycloocta[blindle-5(7H)-carboxylate (6d). The general procedure was followed using ethyl 7-methoxy-4H-furo[3,2-b]-indole-4-carboxylate 5d (52.0 g, 0.2 mmol) and 2-bromocyclopentan-1-one 2a (460 mg, 0.28 mmol) for 2 h at rt. The purification of the crude by flash chromatography (SiO2, hexane/ethyl acetate 9:1 to 8:2) yielded 6d (50 mg, 73%) as a white solid (mp 118–122 °C). H NMR (300 MHz, CDCl3): 7.86 (br s, 1H), 6.99 (dd, J = 2.7 Hz, 1H), 6.90 (dd, J = 9.0, 2.7 Hz, 1H), 5.74 (br s, 1H), 4.96 (dd, J = 4.2, 2.2 Hz, 1H), 4.36 (m, 2H), 3.80 (s, 3H), 2.64 (m, 1H), 2.36 (m, 1H), 2.27 (m, 1H), 2.09 (m, 1H), 2.02–1.82 (m, 2H), 1.37 (s, J = 7.1 Hz, 3H). 13C{1H} NMR (75 MHz, CDCl3): 208.0 (C), 156.5 (C), 151.3 (C), 150.8 (C), 138.8 (C), 129.4 (C), 116.9 (CH), 115.4 (C), 109.3 (CH), 106.9 (CH), 91.7 (CH), 87.4 (CH2), 62.7 (CH2), 56.5 (CH3), 55.7 (CH2), 50.9 (CH), 22.3 (CH2), 21.1 (CH), 14.4 (CH3). ESI(+-)MS m/z (%): 363 (100) [M + Na]+. Anal. Calcd for C24H23NO2C: 76.87; H, 5.30; N, 3.20. Found: C, 77.05; H, 5.31; N, 3.21.

Ethyl 7-Methoxy-8-oxo-9,10,11-tetrahydro-7,11a-epoxy-8,11-methanocycloocta[blindle-5(7H)-carboxylate (6e). The general procedure was followed using ethyl 2-methyl-4H-furo[3,2-b]-indole-4-carboxylate 5e (49.0 g, 0.2 mmol) and 2-bromocyclopentan-1-one 2a (460 mg, 0.28 mmol) for 2 h at rt. The purification of the crude by flash chromatography (SiO2, hexane/ethyl acetate 9:1 to 8:2) yielded 6e (50 mg, 77%) as a white solid (mp 155–160 °C). H NMR (300 MHz, CDCl3): 7.95 (br s, 1H), 7.43 (m, 1H), 7.37 (m, 1H), 7.10 (td, J = 7.5, 0.9 Hz, 1H), 6.53 (br s, 1H), 4.36 (m, 2H), 2.45 (m, 1H), 2.30 (m, 1H), 2.21 (m, 1H), 2.10 (m, 1H), 1.95–1.80 (m, 2H), 1.50 (s, 3H), 1.39 (s, J = 7.1 Hz, 3H). 13C{1H} NMR (75 MHz, CDCl3): 208.6 (C), 151.3 (C), 150.0 (C), 145.0 (C), 130.5 (CH), 128.6 (C), 124.2 (C), 123.2 (CH), 116.2 (CH), 110.6 (CH), 93.5 (C), 91.3 (C), 62.8 (CH), 55.4 (CH2), 54.5 (CH), 21.3 (CH2), 21.1 (CH), 19.8 (CH3), 14.4 (CH3). ESI(+-)MS m/z (%): 348 (100) [M + Na]+. Anal. Calcd for C24H22NO2C: 70.14; H, 5.89; N, 4.31. Found: C, 68.78; H, 5.88; N, 4.37.

Ethyl 8,10-Dimethyl-9-oxo-7,8,9,10-tetrahydro-5H-7,10a-epoxy cycliclohepta[blindle-5(7H)-carbonylethyl (6f). The general procedure was followed using ethyl 4H-furo[3,2-b]-indole-4-carboxylate 5a (46.0 g, 0.2 mmol) and 4-chloro-2,3-dimethylthiophene-2-carboxylic acid (2f) (82.0 mg, 0.5 mmol) and DIPEA (52.3 μL, 0.33 mmol, 1.5 equiv) was added, and the mixture was stirred for 1 at room temperature. The solvent was then removed, and the crude was purified by column chromatography to yield the corresponding products 8–10.

Ethyl 3-(Benzyloxy)-1,1,4-trimethyl-2-oxo-2,3,4,10b-tetrahydroazepino[4,5-b]indole-6(1H)-carboxylate (8) and Ethyl 3-(Benzyloxy)-3,3-dimethyl-2-oxo-8a-(prop-1-en-1-yl)-2,3,3a,8a-tetrahydropyrollo[2,3-b]indole-8(1H)-carboxylate (9). The general procedure was followed using ethyl (E)-2-(prop-1-en-1-yl)-1H-indole-1-carboxylate 1a (46.0 mg, 0.2 mmol) and N-(benzyl)-2-bromo-2-methylpropanamid 7 (82.0 mg, 0.3 mmol, 1.5 equiv) in HFIP (0.84 mL, 0.25 M), DIPEA (52.3 μL, 0.33 mmol, 1.5 equiv) was added, and the mixture was stirred for 1 at room temperature. The solvent was then removed, and the crude was purified by column chromatography to yield the corresponding products 8–10.
6.73 (td, J = 7.1 Hz, 3H), 7.30 (m, 2H), 7.15 (ddt, J = 10.1, 8.4, 1.8 Hz, 4H), 7.10 (m, 4H), 6.92 (t, J = 7.2 Hz, 1H), 6.47 (t, J = 3.5 Hz, 1H), 4.73 (s, 1H), 4.20 (m, 2H), 3.75–3.64 (m, 2H), 2.65 (m, 1H), 2.25 (s, 3H), 1.70 (m, 1H), 1.51–1.31 (m, 1H), 1.28 (s, 3H), 0.88 (t, J = 7.1 Hz, 3H), 13C{1H} (75 MHz, CDCl3): 152.8 (C), 153.5 (C), 146.3 (C), 139.1 (C), 136.2 (C), 129.6 (2 × CH2), 129.5 (CH2), 129.3 (C), 127.6 (2 × CH3), 123.0 (CH1), 121.2 (CH2), 119.4 (CH), 116.1 (CH), 66.0 (CH), 61.8 (CH), 56.9 (CH), 50.3 (CH), 48.2 (CH), 21.3 (CH3), 20.7 (CH2), 20.2 (CH2), 14.2 (CH2), ESI(+)-MS m/z (%): 126 (100) [M + H]+. Anal. Calcld: for C22H21NO: C, 83.78; H, 6.71; N, 4.44. Found: C, 83.35; H, 6.70; N, 4.46.

Ethyl 12-Oxo-7-(p-tolyl)-6,7,8,9,10,11-hexahydro-5H-8,11-methanocycloocta[b]indole-5-carboxylate (16). To a stirring solution of 3d (50.0 mg, 0.13 mmol) in EtOH (1.3 mL, 0.1 M), 0.1 M NaBH4 (4.90 mg, 0.13 mmol) was added, and the mixture was stirred for 2 h at room temperature. The reaction mixture was then quenched with NaHCO3 saturated solution (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over Na2SO4 filtered, and concentrated to yield 16 (33 mg, 65%) as a white solid (mp 135–139 °C). 1H NMR (300 MHz, CDCl3): 8.00 (m, 1H), 7.53 (m, 1H), 7.30–7.23 (m, 4H), 7.16 (m, 2H), 4.45 (q, J = 7.14, 2H), 4.11 (m, 1H), 3.69–3.51 (m, 3H), 2.85 (m, 1H), 2.50 (m, 2H), 2.35 (m, 4H), 2.23–2.11 (m, 2H), 1.45 (t, J = 7.1 Hz, 3H), 13C{1H} (75 MHz, CDCl3): 215.8 (C), 152.2 (C), 141.5 (C), 136.4 (C), 135.4 (C), 129.3 (2 × CH2), 128.1 (C), 126.8 (2 × CH2), 124.4 (2 × CH2), 123.0 (CH2), 119.8 (CH2), 117.8 (CH2), 115.4 (CH3), 63.3 (CH3), 53.7 (CH), 49.0 (CH2), 43.5 (CH3), 28.4 (CH3), 21.8 (CH2), 20.2 (CH2), 14.3 (CH2). ESI(+)-MS m/z (%): 390 (100) [M + H]+. Anal. Calcld: for C27H20NO: C, 77.09; H, 6.99; N, 3.60. Found: C, 76.91; H, 7.01; N, 3.61.

Ethyl 2-(3-Cyclopentenyl)-4-fluoro-3,2-b-dindle-4-carboxylate (17). To a stirring solution of 6a (47.0 mg, 0.15 mmol) in CHCl3 (0.75 mL, 0.2 M), pTSAH (3.00 mg, 0.015 mmol) was added, and the mixture was stirred for 1.5 h at room temperature. The reaction mixture was concentrated, and the crude was purified by column chromatography (SiO2, hexane/ethyl acetate 8:2) to yield 17 (44 mg, 85%) as a colorless solid (mp 188–190 °C).
94%) as a pink solid (117–119 °C). 1H NMR (500 MHz, CDCl3): 8.33 (br s, 1H), 7.63 (m, 1H), 7.34–7.25 (m, 2H), 6.68 (s, 1H), 4.53 (q, J = 7.1 Hz, 2H), 3.59 (dd, J = 10.6, 8.5 Hz, 1H), 2.57 (m, 1H), 2.50 (dd, J = 18.8, 8.5, 3.5 Hz, 1H), 2.44 (dd, J = 10.1, 8.5 Hz, 1H), 2.36 (m, 1H), 2.25 (m, 1H), 2.00 (m, 1H), 1.52 (t, J = 7.1 Hz, 3H), 1.38 (CH2), 29.6 (CH2), 21.0 (CH2), 14.5 (CH3).

**Notes**

The authors declare no competing financial interest.

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