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Synthesis of Indole-Derived Allocolchicine Congeners through Pd-Catalyzed Intramolecular C-H Arylation Reaction

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The synthesis of several new heterocyclic structural analogs of the natural antimitotic agent allocolchicine is reported. As a key step an intramolecular Pd-catalyzed C–H arylation reaction was used to close the seven-membered ring fused with two electron-rich aryl fragments. The stereostructure of the target compounds was determined by X-ray crystal analysis. The primary biological assessment of the synthesized compounds was carried out on human lymphoma cells. Several allocolchicinoids were determined to possess antiproliferative and apoptosis-inducing activity in the micromolar concentration range.

Introduction

Microtubules play an essential role in many vital cellular functions of eukaryotic cells such as the development and maintenance of cell shape, cell signaling, and, importantly, cell proliferation.[1] They are formed in a dynamic polymerization/de-polymerization process that involves α- and β-tubulin protein subunits. Interference with this dynamic equilibrium leads to cell cycle arrest and, consequently, to apoptotic cell death. For this reason, the targeting of microtubule dynamics is regarded as a successful strategy for the treatment of cancer.[2]

The cytostatic drug colchicine (**1**; Figure 1) isolated from *Colchicum autumnale* was the first tubulin destabilizing agent discovered.[3] Although colchicine is clinically approved for the treatment of acute gout and familial Mediterranean fever, a high general toxicity has hampered its application in cancer chemotherapy.[4] However, some natural structural analogs of colchicine (**1**), such as allocolchicine (**2**)[5] and combretastatin A-4 (CA-4; **3**;[6] Figure 1), represent important lead structures in the design of new antimitotics that address the colchicine binding site of tubulin.[3d,7]

During the past decade a number of tubulin polymerization inhibitors have been reported that are characterized by the presence of an indole nucleus as a key pharmacophore. Most of them (e.g. **3** and **4**) are structurally related to CA-4 (Figure 2).[8]

Dauban, Dodd, and co-workers synthesized a series of C5-alkylated indolobenzazepinones (for instance compound **5**) related to allocolchicine (**2**), some of which exhibited potent antimitotic activity across a wide panel of cancer-cell lines. In the course of our own research into colchicinoids, we recently described the synthesis of indole-derived allocolchicine analogs **6** and **7**.[9] These compounds exhibited strong antiproliferative and apoptosis-inducing activities (at nanomolar or even sub-nanomolar concentrations) against Burkitt-like lymphoma (BJAB) cells, although their unspecific cytotoxicity was found to be particularly low. The most potent compound, *rac*-**7** (X = OH), also caused high levels of apoptosis induction in several types of chronic lymphocytic leukemia (CLL) cells including primary cell lines. The cytotoxicity of **7** towards primary CLL cells was found to be superior to that of vincristine, a clinically approved drug for the treatment of CLL.[10]

The discovery of highly active heterocyclic allocolchicine congeners challenged us to further extend the library of available compounds and to explore their antimitotic properties. Within this paper, we report the synthesis of two indole-derived allocolchicinoids *rac*-**9** and *rac*-**10** (Figure 3), which represent constitutional isomers to **6** and **7**, respectively, with a different mode of indole fragment fusion.

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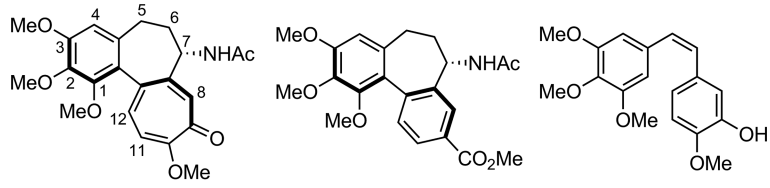


Figure 1. Selected natural antimitotic agents that interact with the colchicine-binding site of tubulin.

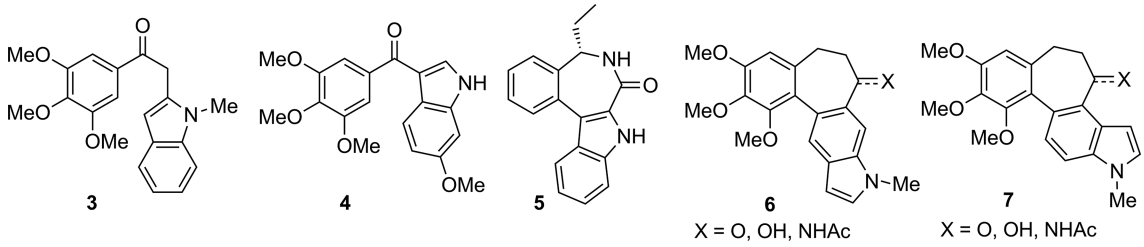


Figure 2. Synthetic antimitotics that possess an indole pharmacophore.

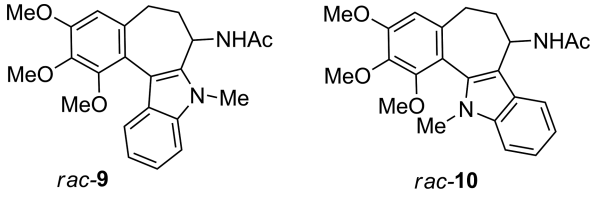
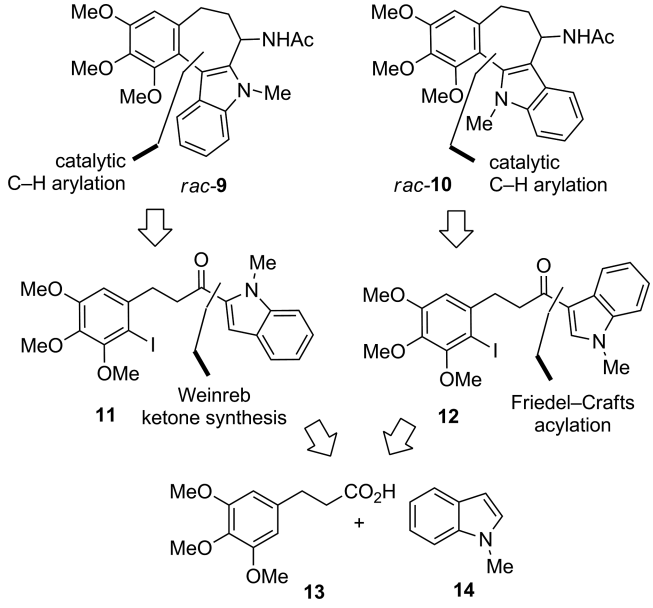


Figure 3. Indole-derived allocolchicinoids *rac*-**9** and *rac*-**10** as target compounds in the present study.

Results and Discussion

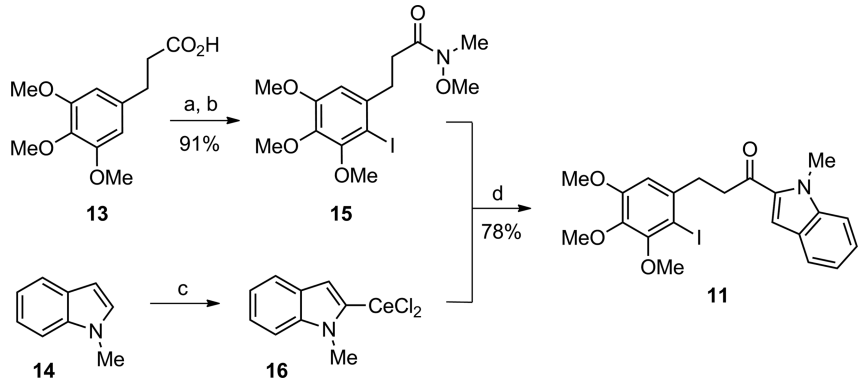
The formation of a fused seven-membered ring is the main challenge in allocolchicine synthesis and several approaches to its construction have been proposed.[11] Taking into account the electron-rich nature of the indole moiety, we followed the strategy initially proposed by Fagnou and co-workers in the course of their total synthesis of allocolchicine (**2**). Thus, we envisaged that the tetracyclic scaffold of both *rac*-**9** and *rac*-**10** could be formed by direct intramolecular C–H arylation reaction[12] of aryl iodides **11** and **12**, respectively (Scheme 1). Precursor **11** might be accessible through a Weinreb ketone synthesis[13] by starting from commercial acid **13** and 1-methyl-1*H*-indole (**14**). Substrate **12** could be formed through Friedel–Crafts acylation reaction of **14**[14] with a suitably functionalized acylation reagent, again derived from **13**.



Scheme 1. Strategy for the synthesis of the indole-derived allocolchicinoids *rac*-**9** and *rac*-**10**.

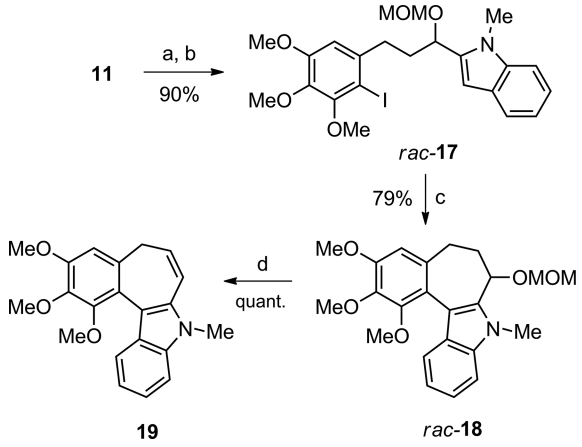
Our synthesis of allocolchicinoid *rac*-**9** started with conversion of dihydrocinnamic acid derivative **13** into Weinreb amide **15** through acylation of *N*,*O*-dimethylhydroxylamine with the acyl chloride formed in situ from **13**, and subsequent iodination of the resulting amide in the presence of silver trifluoroacetate (Scheme 2).[15] Reaction of **15** with organocerium reagent[16] **16** prepared in situ from **14** by metallation with *t*BuLi and transmetallation with $CeCl_3$, consistently afforded cyclization precursor **11** in 78% yield. It is worth nothing that high yields were only obtained under thoroughly optimized conditions (immediate use of unstable intermediate **16** generated in situ at 0 °C).

Ketone **11** was readily transformed into methoxymethyl (MOM) protected alcohol *rac*-**17** (Scheme 3), which smoothly underwent Pd-catalyzed intramolecular C–H arylation reaction under the conditions reported by Fagnou and co-workers.[11d] This afforded tetracyclic product *rac*-**18** in 79% yield along with minor amounts of by-product that resulted from reductive dehalogenation of *rac*-**17**. However, as all attempts to achieve MOM-deprotection of *rac*-**18** led



Scheme 2. Synthesis of intermediate **11**. *Reagents and conditions:* (a) $(COCl)_2$, THF, room temp., 12 h, then HN(OMe)Me·HCl, pyridine, 0 °C; (b) I_2, $AgOC(O)CF_3$, CH_2Cl_2, room temp., 3 h; (c) *t*BuLi, THF, –5 to 0 °C, 10 min, then $CeCl_3$, THF, ca. 30 s; (d) THF, 0 °C to room temp., 10 min, then aqueous NH_4Cl.

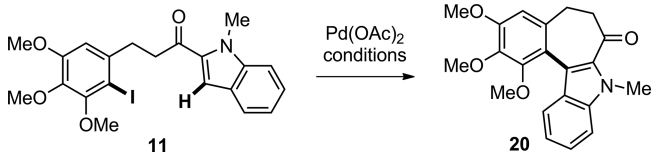
to the rapid formation of alkene **19** we returned to unprotected ketone **11** as another potential substrate for the intramolecular C–H arylation reaction.



Scheme 3. Attempted synthesis of *rac*-**9** through intramolecular C–H arylation reaction of MOM-protected substrate *rac*-**17**. *Reagents and conditions:* (a) $NaBH_4$, THF/MeOH, room temp.; (b) CH_3OCH_2Cl, $(iPr)_2NEt$, THF, reflux, 3 h; (c) $Pd(OAc)_2$ (10 mol-%), DavePhos (10 mol-%), K_2CO_3 (2 equiv.), 130 °C, 12 h; (d) HCl (trace), MeOH, 0 °C or pyridinium *p*-toluenesulfonate, 2-butanol, room temp.; DavePhos = 2-dicyclohexylphosphino-2′-dimethylamino-1,1′-biphenyl.

Screening of several catalytic systems (Table 1) revealed that under ligand-free (Jeffery's) conditions[17] in the presence of $Pd(OAc)_2$, Cs_2CO_3 and pivalic acid[18] in dimethylformamide (DMF) tetracyclic derivative **20** is formed from **11** in 71% yield (Table 1, Entry 10). The accelerating effect of cesium pivalate on this transformation suggests that it proceeds through a concerted metallation–deprotonation pathway.[19] The major side reaction is the Pd-mediated dehydrogenation of ketone **20** to the corresponding enone. As Saegusa-type oxidations require a stoichiometric oxidant, such as Ag_2CO_3/TEMPO,[20] quinone,[21] chlorobenzene[22] or an organic peroxide,[23] the formation of the dehydrogenation by-product (in the synthesis of **20**) could be minimized by careful solvent deoxygenation and by lowering the reaction temperature to 85 °C.

Table 1. Direct intramolecular C–H arylation reactions of indolyl ketone **11**.

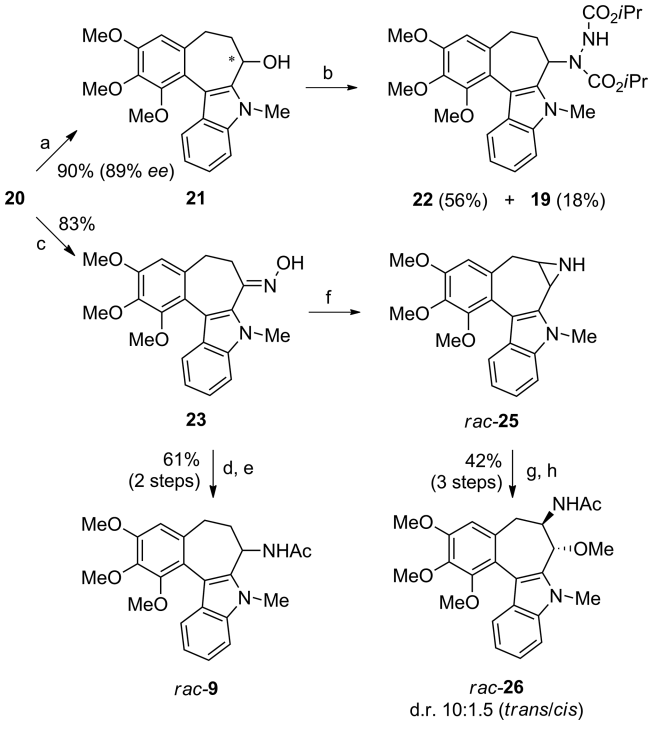


Entry[a]	Ligand	Ligand/[Pd] ratio	Additive	*T* [°C]	Yield of **20** [%][b]
1[c]	DavePhos	1:1	K_2CO_3	120	15
2	PPh_3	2:1	Ag_2CO_3	100	18
3[c]	PPh_3	2:1	AgOAc	120	–
4[c]	PPh_3	2:1	KOAc	120	48
5	$P(tBu)_3$·HBF_4	2:1	K_2CO_3/KOAc	120	28
6	PCy_3·HBF_4	2:1	K_2CO_3/KOAc	120	13
7	–	–	KOAc	120	24
8	–	–	CsOPiv[d]	120	30
9	–	–	CsOPiv[d]	85	65
10[c]	–	–	CsOPiv[d]	85	71

[a] All reactions were carried with $Pd(OAc)_2$ (5 mol-%) in anhydrous DMF (0.1 M) in a vial equipped with a Teflon® mininert® valve until full conversion of the starting material (as determined by TLC). [b] Isolated yields. [c] 10 mol-% of $Pd(OAc)_2$ was used. [d] Prepared in situ by mixing Cs_2CO_3 and pivalic acid.

Tetracyclic ketone **20** was subsequently used in a series of functional group transformations (Scheme 4). Among the methods examined for asymmetric ketone reduction [(*R*)-BINOL/$LiAlH_4$,[24] (+)-TarBNO$_2$/$LiBH_4$,[25] CBS reduction[26]], reaction of **20** with BH_3·tetrahydrofuran (THF) in the presence of catalyst (*S*)-Me-CBS[26] produced the best results, by yielding alcohol **22** in 90% yield with 89% *ee*.

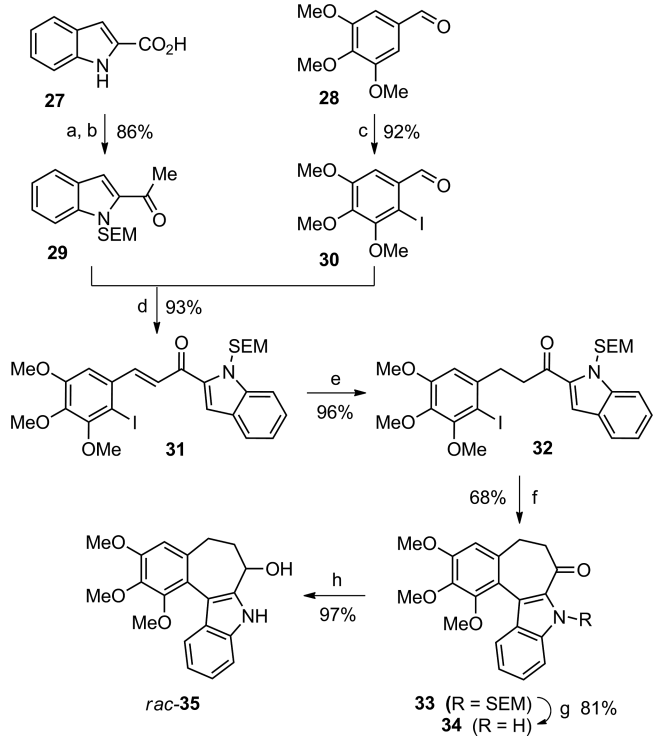
Treatment of **21** with $Zn(N_3)_2$·2Py[27] or trimethylsilyl azide[28] under Mitsunobu conditions did not yield the corresponding azide. Instead, a mixture of elimination product **19** and diisopropyl azodicarboxylate (DIAD) adduct **22** was obtained. To access desired acetamide *rac*-**9** we therefore returned to ketone **20** and first converted it into oxime **23**. Reduction of **23** with $NaBH_4/NiCl_2$ (nickel boride-catalyzed hydrogenation)[29] to corresponding amine *rac*-**24** (not shown) and subsequent acylation with Ac_2O/pyridine gave



Scheme 4. Synthesis of allocolchicinoids *rac*-**9** and *rac*-**26**. *Reagents and conditions:* (a) (*S*)-Me-CBS (1.25 equiv.), $H_3B{\cdot}THF$ (1 equiv.), –30 °C, 1 h; (b) $Zn(N_3)_2{\cdot}2Py$, DIAD, PPh_3, toluene, room temp., 0.5 h; (c) $NH_2OH{\cdot}HCl$, pyridine, EtOH, reflux, 24 h; (d) $NaBH_4$, $NiCl_2$, MeOH, room temp., 12 h; (e) Ac_2O, pyridine, CH_2Cl_2, 0 °C; (f) $LiAlH_4$, THF, reflux, 2 h; (g) silica gel, CH_2Cl_2/MeOH, 10:1; (h) Ac_2O, pyridine, CH_2Cl_2, 0 °C.

desired allocolchicinoid *rac*-**9** in 51% yield over 3 steps. Interestingly, when reduction of oxime **23** was carried out with $LiAlH_4$ in THF at reflux temperatures,[30] aziridine *rac*-**25** was obtained as a major product (probably formed through a nitrene intermediate).[31] Chromatographic purification of *rac*-**25** on silica gel (with CH_2Cl_2/MeOH) followed by acetylation of the resulting α-methoxyamine gave amide *rac*-**26** as a mixture of diastereomers (*trans*/*cis* = 7:1) in 42% yield over 3 steps. The structure of *rac*-**26** was confirmed by 2D NMR spectroscopy correlations and HRMS analysis.

In addition to *N*-methyl-protected allocolchicinoids **20**, **21**, **23**, *rac*-**9** and *rac*-**26**, two analogs with a free NH group were prepared by starting from commercial 1*H*-indole-2-carboxylic acid (**27**) and 3,4,5-trimethoxybenzaldehyde (**28**) by following a slightly different synthetic approach (Scheme 5). Thus, substrate **27** was first transformed into ketone **29** by reaction with an excess of MeLi in ether[32] followed by 2-trimethylsilyl)ethoxymethyl ester (SEM)-protection of the NH group. Second building block **30** was prepared from aldehyde **28** by iodination with *N*-iodosuccinimide in the presence of catalytic amounts of trifluoroacetic acid (TFA).[33] Aldol condensation of **29** and **30** under basic conditions readily afforded enone **31** in 93% yield. Conjugate reduction of **31** to **32** (which tolerated the easily cleavable aryl iodide functionality) was achieved in 96% yield with Stryker's reagent $[HCu(PPh_3)]_6$ in the presence of stoichiometric water.[34] The use of other reagents known to perform well in the hydrogenation reactions of chalcone-type substrates [e.g. $LiAlH_4$/CuI,[35] catecholborane,[36] or H_2/Pd(C)/Ph_2S[37]] only led to mixtures of over-reduction products in this case. Only high-pressure hydrogenation of **31** in the presence of Adams's catalyst (50 atm H_2, 10 mol-% PtO_2, EtOAc, 5 d) also afforded **32** in a reasonable yield of 75%.

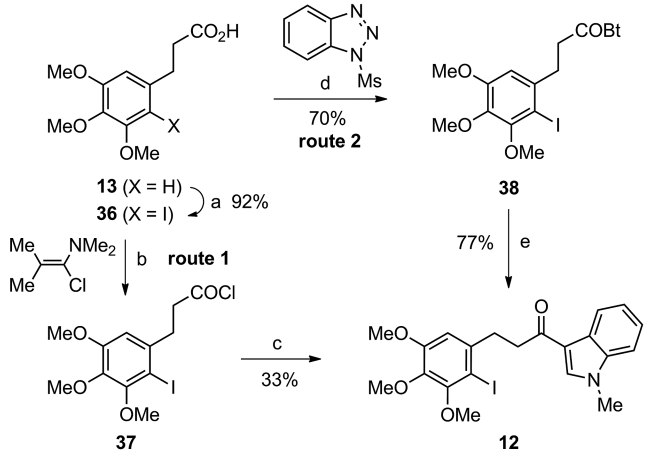


Scheme 5. Synthesis of allocolchicinoids **34** and *rac*-**35**. *Reagents and conditions:* (a) MeLi, Et_2O, 35 °C, 3 h; (b) NaH, DMF, 0 °C to room temp., 1 h, then 2-(trimethylsilyl)ethoxymethylchloride, 0 °C, 1 h; (c) *N*-iodosuccinimide, TFA, MeCN, room temp., 3 d; (d) NaOH (2 M), EtOH, room temp., 12 h; (e) $[(Ph_3P)CuH]_6$ (0.31 equiv.), H_2O (1 equiv.), benzene, room temp., 6 h; (f) $Pd_2(dba)_3{\cdot}CHCl_3$ (10 mol-%), CsOPiv (3 equiv.), DMF, 90 °C, 6 h; (g) HCl (2 M), EtOH, reflux, 3 h; (h) $NaBH_4$, THF/MeOH, room temp.

The subsequent intramolecular C–H arylation reaction of **32** took place in the presence of 10 mol-% $Pd_2(dba)_3{\cdot}CHCl_3$ and an excess of CsOPiv in DMF in a sealed vial at 90 °C to afford tetracyclic product **33** in 68% yield (Scheme 5). Treatment of **33** with hydrochloric acid (0.5 M) in water/ethanol (1:4) resulted in clean SEM deprotection and provided 81% of ketone **34**, which was further reduced with $NaBH_4$ to give alcohol *rac*-**35**. This way, allocolchicinoids **34** and *rac*-**35** were synthesized from 1*H*-indole-2-carboxylic acid **27** in 6 or 7 steps, respectively, with an overall yield of > 40%.

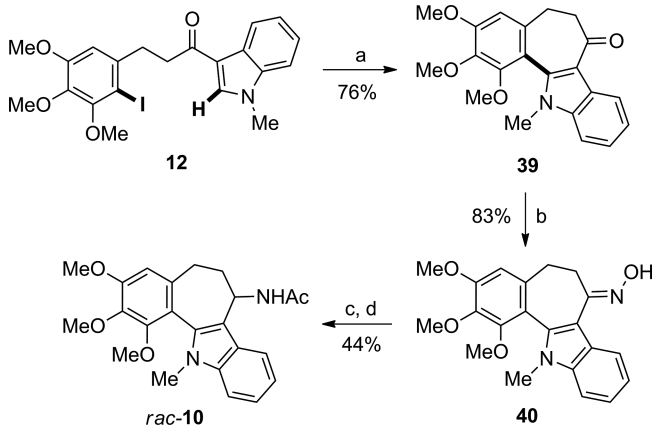
The next task was the synthesis of allocolchicinoid *rac*-**10** that displays a different structural arrangement (Scheme 1). For this purpose, dihydrocinnamic acid **13** was first iodinated with I_2/$AgOC(O)CF_3$ (Scheme 6). Product **36** was then converted with $(COCl)_2$ to acyl chloride **37** that was used in situ in the subsequent indole acylation step

(Scheme 6, route 1). However, the proposed Friedel–Crafts reaction, by using either indole or *N*-methylindole (**14**), was difficult. Under a variety of conditions[14a–14d,14i] mostly oligomerization product mixtures[38] were obtained. We also noted that the conversion of acid **36** into acid chloride **37** proceeded only in moderate yield because de-iodination was occurring as a side reaction. However, by switching from oxalylchloride to (1-chloro-2-methylpropenyl)dimethylamine (Ghosez reagent)[39] and by using $EtAlCl_2$[14c] as a HCl-scavenging Lewis acid desired product **12** was obtained in at least 33% yield. Even better results were obtained by employing a mild benzotriazole-derived acylating reagent.[14f] Thus, reacting acid **36** with 1-(methylsulfonyl)-1*H*-benzotriazole in the presence of triethylamine afforded **38**, which on treatment with indole **14** in the presence of $TiCl_4$ in dichloromethane readily afforded cyclisation precursor **12** in 54% yield over 2 steps (Scheme 6, route 2).



Scheme 6. Synthesis of cyclisation precursor **12**. *Reagents and conditions:* (a) I_2, $AgOC(O)CF_3$, CH_2Cl_2, room temp., 3 h; (b) Ghosez reagent (1.1 equiv.), CH_2Cl_2, room temp., 3 h; (c) $EtAlCl_2$ (1 M) in hexane, CH_2Cl_2, room temp., 5 min; (d) 1-mesyl-1,2,3-benzotriazole, Et_3N, THF, reflux, 12 h; (e) **14**, $TiCl_4$ (2 equiv.), CH_2Cl_2, 0 °C, 0.5 h.

The cyclisation of aryl iodide **12** by intramolecular C–H arylation reaction then proceeded smoothly in the presence of 10 mol-% of $Pd(OAc)_2$, excess Cs_2CO_3 and pivalic acid in DMF to afford tetracyclic ketone **39** in 76% yield (Scheme 7). In contrast to the synthesis of **20** and **33**, almost no side dehydrogenation of **39** to the corresponding enone occurred even at elevated temperatures (up to 110 °C). Completion of the synthesis of *rac*-**10** was achieved through first converting ketone **39** into oxime **40**, reduction of the latter with $NaBH_4/NiCl_2$ in methanol and acylation of the resulting amine with acetic anhydride. By following this method allocolchicinoid *rac*-**10** was obtained in 36% yield over three steps. The lowest-yielding step was oxime reduction, however, application of alternative reductants (Zn/HCO_2NH_4,[40] Na/*i*PrOH,[30] $LiAlH_4$,[30] BH_3·THF[41]) proved much less efficient. In particular, attempts to achieve the reductive amination of ketone **39** with $NH_4OAc/NaBH_3CN$[42] or by using a Rh-catalyzed Leukart-Wallach-type amination reaction[43] resulted mainly in the recovery of starting material.



Scheme 7. Completion of the synthesis of allocolchicinoid *rac*-**10**. *Reagents and conditions:* (a) $Pd(OAc)_2$ (10 mol-%), Cs_2CO_3 (3 equiv.), PivOH (2.5 equiv.), DMF, 110 °C, 24 h; (b) NH_2OH·HCl, pyridine, EtOH, reflux, 24 h; (c) $NaBH_4$, $NiCl_2$, MeOH, room temp., 24 h; (d) Ac_2O, pyridine, CH_2Cl_2, 0 °C.

One should note that [similarly to allocolchicine (**2**) and previously synthesized allocolchicinoids **6** and **7**] two diastereomeric atropisomers are observed in the ^1H and ^{13}C NMR spectra of compounds *rac*-**9**, *rac*-**10**, **21**, *rac*-**25**, and *rac*-**35** at ambient conditions.[11c,11e,11g,11i,44] The ratio of atropisomers varies with the polarity of the solvent used, possibly as a consequence of solvation effects.[44] A chromatographic separation of atropisomers proved impossible even in the case of *rac*-**10** for which rotation around the aryl–aryl axis is expected to be most hindered.

Finally, we investigated the stereostructure of tetracyclic ketones **20** and **34** by using X-ray crystallography (Figure 4). The geometric parameters of **20** and **34** were found to be considerably different. The dihedral angle between aromatic fragments **A** and **B** (see Figure 4) was determined as 43.0° for **20** and 32.3° for **34**, relative to 54° for colchicine (**1**)[45] and 47° for **7** (X = O).[9] These data suggest that compound **34** does not meet the basic structural requirements for interaction with the colchicine binding site of tubulin,[3d] whereas **20** shows structural similarity with highly active **7** (X = O).

The anti-tumoral potential of the compounds synthesized was assessed by determining their antiproliferative and apoptosis-inducing activities against BJAB cells.

The results, displayed in Table 2, suggest that compounds **20**, **21**, **23**, and *rac*-**9** exhibit IC_{50}/AC_{50} values only in the lower micromolar concentration range, whereas **34** and *rac*-**35** were found to be virtually inactive. Thus, in comparison to the "isomeric" series (e.g. of type **6** and **7**) the compounds prepared in the course of the present study proved to be less active by a factor of about 1000. The cytotoxicity of allocolchicinoids **39**, **40**, *rac*-**10** (not shown in Table 2) was assessed by using AsPC-1 (human adenocarcinoma) and HaCaT cell lines. The compounds of this series did not

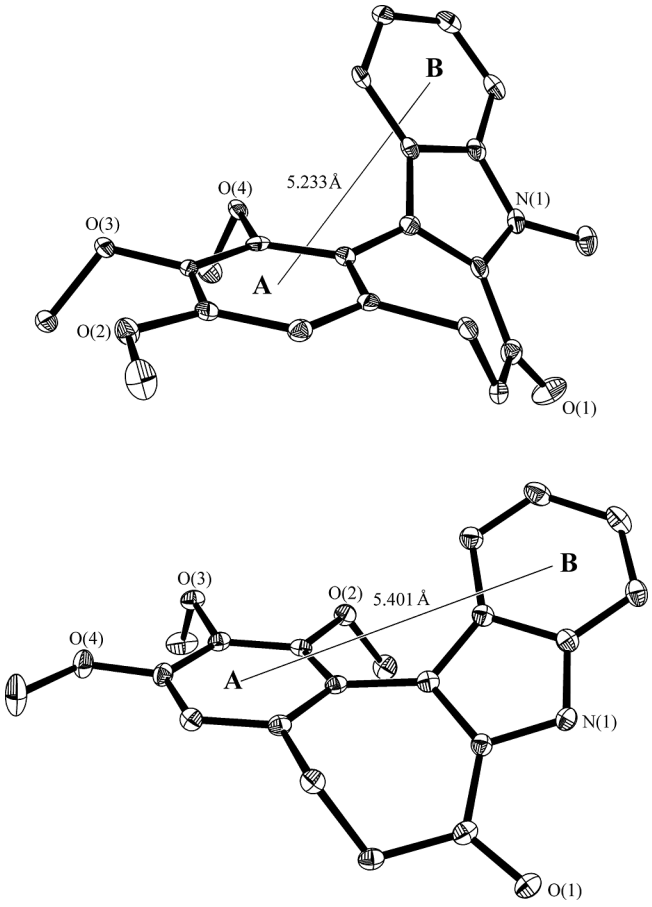


Figure 4. Molecular structures of ketones **20** (top) and **34** (bottom) in the crystalline state; H atoms are omitted for clarity.

exhibit notable antiproliferative activity in concentrations up to 100 μM.

Table 2. Antitumor activity of allocolchicinoids *rac*-**9**, **20**, **21**, **23**, **34**, and *rac*-**35** against BJAB tumor cells.

	20	**21**	**23**	*rac*-**9**	**34**	*rac*-**35**
IC_{50}[a] [μM]	3	10	1	0.5	> 100	> 100
AC_{50}[b] [μM]	5	10	5	0.5	> 100	> 100

[a] The proliferation inhibition (IC_{50}) after 24 h was determined by using a CASY cell counter. [b] Apoptosis induction (AC_{50}) was determined after 72 h by measuring the DNA fragmentation at the single-cell level.

Conclusions

In conclusion, we have successfully elaborated the synthesis of two new structural types of indole-derived allocolchicine congeners with different modes of heterocyclic ring fusion and various functionalities at C(7)-position. The construction of the specific tetracyclic ring system was achieved through Pd-catalyzed intramolecular C–H arylation reaction of suitably functionalized indolyl ketones as a key step. The structure of two allocolchicinoids was investigated by means of X-ray crystallography. The synthesized compounds extend our library of indolo-allocolchicinoids and four new compounds were found to possess pronounced antiproliferative and apoptosis-inducing activity in the micromolar concentration range. Also, it cannot be excluded that the natural product-like structures possess other, yet unidentified, biological properties not associated with the inhibition of cell proliferation.

Experimental Section

General Information: All moisture sensitive reactions were carried out under an argon atmosphere by using Schlenk and needle/syringe techniques. Glassware was flame dried under vacuum (0.5–1 mbar) and cooled under an argon atmosphere. Syringes, needles and transfer cannulas were dried in an oven at 100 °C and were flushed with argon directly prior to use. Solvent preparations were carried according to described procedures.[46] Petroleum ether refers to a fraction with boiling temperature 40–70 °C. Flash chromatography was performed with silica 60 (230–400 mesh) supplied by Merck. ^{1}H NMR spectra were recorded with a Bruker DRX 500, Bruker AV 400, Agilent DD2 400, or Bruker DPX 300 instruments. Chemical shifts are reported relative to the solvent reference as an internal standard (δ = 7.26 ppm for $CDCl_3$; δ = 3.31 ppm for CD_3OD; δ = 1.72 ppm for [D_8]THF). ^{13}C NMR spectra were recorded with a Bruker DRX 500 (126 MHz), Bruker AV 400 (100 MHz), Agilent DD2 400 (100 MHz) or Bruker DPX 300 (75 MHz) instruments with complete proton decoupling. Chemical shifts are reported relative to the solvent reference as the internal standard (δ = 77.16 ppm for $CDCl_3$; δ = 67.21 ppm for [D_8]THF; δ = 49.00 ppm for CD_3OD). The assignments for ^{1}H NMR spectroscopic signals are supported by HMBC, HMQC(HSQC), and H,H-COSY spectra. Infrared spectra (FTIR) were recorded with a Perkin–Elmer FTIR Paragon 1000 or Shimadzu IRPrestige-21 spectrometer by using Fourier transform infrared (FTIR) attenuated total reflection (ATR) technique. Melting points were measured with a Büchi B-545 melting point apparatus. Mass spectra were recorded with a Finnigan Incos 50 Galaxy System or Polaris Q/Trace GC Ultra (DIP-MS). High-resolution mass spectra were recorded with a Finnigan MAT 900 (HRMS-EI). Compounds **15**, **29**, and **30** were synthesized according to previously reported procedures.[15,32,33]

The crystallographic data were collected with a SMART APEX (compound **20**) and Nonius-Kappa Apex (compound **34**) diffractometers (graphite-monochromated, Mo-K_α-radiation, ω-scan technique, λ = 0.71073 Å) at 100 K. The structures were solved by direct methods and were refined with F^2 with the SHELXTL package.[47] All non-hydrogen atoms were found from Fourier syntheses of electron density and were refined anisotropically. All H atoms in **20** and **34** (except H1A in **34**) were placed in calculated positions and were refined in the riding model. The H1A atom in **34** was found from Fourier syntheses of electron density and was refined anisotropically. SADABS[48] was used to perform area-detector scaling and absorption corrections.

Compound 20 ($C_{21}H_{21}NO_4$): a = 16.3683(12) Å, b = 24.6692(19) Å, c = 8.5005(6) Å, orthorhombic, space group Pccn, Z = 8, V = 3432.4(4) Å^3, d_{BbIy} = 1.360 g cm^{-3}, μ = 0.094 mm^{-1}, F(000) = 4936, 1.49° ≤ θ ≤ 26.0°, $R1$ = 0.0772 and $wR2$ = 0.1273 [$I > 2\sigma(I)$], $R1$ = 0.1474 and $wR2$ = 0.1442 (all data), $S(F^2)$ = 1.040, largest diff. peak and hole 0.287 and –0.311 e Å^{-3}.

Compound 34 ($C_{20}H_{19}NO_4$): a = 10.7160(5) Å, b = 11.9565(7) Å, c = 13.0681(5) Å, β = 100.556(3)°, monoclinic, space group $P2_1/c$, Z = 4, V = 1646.02(14) Å^3, d_{BbIy} = 1.361 g cm^{-3}, μ = 0.095 mm^{-1},

$F(000)$ = 712, 1.39° ≤ θ ≤ 26.99°, $R1$ = 0.0405 and $wR2$ = 0.0901 [$I > 2\sigma(I)$], $R1$ = 0.0689 and $wR2$ = 0.0980 (all data), $S(F^2)$ = 1.009, largest diff. peak and hole 0.189 and –0.217 e Å^{-3}.

CCDC-1018384 (for **20**) and -1018383 (for **34**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

3-(2′-Iodo-3′,4′,5′-trimethoxyphenyl)-1-(1′′-methyl-1*H*-indol-2′′-yl)propan-1-one (11): $CeCl_3$ (2 g, 8.14 mmol) was dried under reduced pressure (ca. 1 × 10^{-2} Pa) for 3 h as the temperature was slowly increased to 140 °C, then cooled to room temp. Anhydrous THF (20 mL) was added and the resulting suspension was stirred vigorously for 12 h followed by cooling to –5 °C. 1-Methyl-1*H*-indole (**14**; 1 g, 7.63 mmol) was dissolved in anhydrous THF (10 mL) under an argon atmosphere. The solution was cooled to –5 °C and *t*BuLi (4.8 mL of 1.7 solution in pentane, 8.14 mmol) was added dropwise. The resulting yellow suspension was stirred for 10 min at –5–0 °C and then added rapidly to the suspension of $CeCl_3$ through a syringe. The reaction mixture was stirred for about 30 seconds and a solution of amide **15** (2.08 g, 5.09 mmol) in anhydrous THF (8 mL) was added in one portion. The stirring was continued for a further 30 min and the reaction was allowed to warm to room temperature. The volatiles were removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (100 mL) and filtered through aluminum oxide (basic, Alox B). The solvent was removed under reduced pressure and the crude reaction mixture was subjected to column chromatography on silica gel (eluent EtOAc/petroleum ether, 1:4) to give compound **11** (1.9 g, 78%) as a colorless oil. R_f = 0.32 (EtOAc/petroleum ether, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.14–3.24 [m, 2 H, CH_2C(O)], 3.25–3.34 (m, 2 H, CH_2Ar), 3.84 (s, 3 H, CH_3), 3.85 (s, 3 H, CH_3), 3.89 (s, 3 H, CH_3), 4.10 (s, 3 H, CH_3), 6.75 (s, 1 H, 6′-H), 7.12–7.18 (m, 1 H, Ar′′*H*), 7.35 (s, 1 H, 3′′-H), 7.38 (d, ^3J = 3.5 Hz, 2 H, Ar′′*H*), 7.68 (d, ^3J = 8.1 Hz, 1 H, Ar′′*H*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 32.3, 36.3, 40.3, 56.3, 60.9, 61.1, 87.9, 109.3, 110.4, 111.7, 120.8, 123.0, 125.9, 126.1, 134.7, 139.6, 140.2, 140.6, 153.3, 153.7, 193.0 ppm. IR (ATR): $\tilde{\nu}$ = 930, 980, 1004, 1044, 1100, 1126, 1163, 1198, 1240, 1270, 1320, 1348, 1386, 1426, 1478, 1512, 1559, 1614, 1656, 1734, 2935 (broad) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 207 (2), 220 (3), 234 (1.5), 248 (2), 262 (2), 280 (4), 294 (3), 310 (4), 322 (3), 352 (100), 479 (1) [M]$^+$. HRMS (EI, 70 eV): *m*/*z* calcd. for $C_{21}H_{22}INO_4$ [M]$^+$ 479.0594; found 479.059.

1′,2′,3′-Trimethoxybenzo[5′,6′:5,4]-6,7-dihydro-1-oxo-1*H*-cyclohepta[2,3-*b*]-1′′-methyl-1*H*-indole (20): The reaction was carried out in a glass vial (10 bar pressure limit) equipped with a mininert® Teflon® valve. Compound **11** (0.4 g, 0.84 mmol), $Pd(OAc)_2$ (19 mg, 0.084 mmol), Cs_2CO_3 (0.82 g, 2.52 mmol) and pivalic acid (214 mg, 2.1 mmol) were suspended in anhydrous degassed DMF (8 mL) under argon atmosphere and the reaction vessel was sealed. The reaction mixture was stirred for 5 h at 85 °C, then cooled to room temp., diluted with EtOAc (50 mL), filtered through a pad of Celite® and concentrated under reduced pressure. After column chromatography on silica gel (eluent EtOAc/acetone/petroleum ether, 1:1:4) compound **20** (209 mg, 71%) was isolated as a pale-yellow solid. R_f = 0.37 (EtOAc/acetone/petroleum ether, 1:1:4), m.p. 179 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.66–2.81 [m, 2 H, CH_2C(O)], 2.95–3.15 (m, 2 H, CH_2Ar), 3.35 (s, 3 H, CH_3), 3.93 (s, 3 H, CH_3), 3.98 (s, 3 H, CH_3), 4.02 (s, 3 H, CH_3), 6.69 (s, 1 H, 4′-H), 7.11–7.18 (m, 1 H, Ar*H*), 7.39–7.42 (m, 2 H, Ar*H*), 7.78 (d, ^3J = 8.2 Hz, 1 H, Ar*H*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 30.7, 32.1, 46.5, 56.2, 60.8, 61.5, 107.5, 109.9, 118.9, 119.0, 120.2, 125.0, 125.4, 125.8, 133.0, 136.9, 139.2, 141.6, 152.5, 152.6, 197.2 ppm. IR (ATR): $\tilde{\nu}$ = 995, 1038, 1080, 1103, 1133, 1157, 1196, 1238, 1259, 1313, 1343, 1369, 1396, 1466, 1496, 1595, 1648 (strong), 1740, 2851, 2932 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 218 (6), 232 (5), 246 (9), 262 (5), 276 (8), 292 (15), 308 (26), 322 (12), 339 (4), 351 (100) [M]$^+$. HRMS (EI, 70 eV): *m*/*z* calcd. for $C_{21}H_{21}NO_4$ [M]$^+$ 351.1471; found 351.148.

1′,2′,3′-Trimethoxybenzo[5′,6′:5,4]-6,7-dihydro-1-hydroxy-1*H*-cyclohepta[2,3-*b*]-1′′-methyl-1*H*-indole (21): (*S*)-3,3-Diphenyl-1-methylpyrrolidino[1,2-*c*]-1,3,2-oxazaborole (150 µL 0.95 in toluene, 0.142 mmol) and H_3B·THF (121 µL, 0.142 mmol) were dissolved in anhydrous THF (1.5 mL) under an argon atmosphere. The reaction mixture was stirred 30 min at room temp., cooled to 0 °C and a solution of ketone **20** (50 mg, 0.142 mmol) in anhydrous THF (1 mL) was added dropwise over 30 min. The reaction mixture was then quenched by slow addition of EtOH (0.5 mL), the reaction was allowed to warm to room temperature and all the volatiles were removed under reduced pressure. After column chromatography on silica gel (eluent EtOAc/petroleum ether, 1:1) compound **21** (45 mg, 90%, 89% *ee*) was obtained as a white solid. The enantiomeric excess value was determined by means of HPLC analysis on a chiral stationary phase (column Chromasil AmyCoat 5 µm, 4.6 × 250 mm, flow 1 mL/min, eluting system heptane/*i*PrOH, 95:5). R_f = 0.28 (EtOAc/petroleum ether, 1:1), m.p. 159 °C. In ^{1}H NMR spectra (CD_3OD) two conformers are observed in 1:0.45 ratio.[49] Major: ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 1.98–2.68 (m, 4 H, CH_2), 3.39 (s, 3 H, CH_3), 3.84 (s, 3 H, CH_3), 3.85 (s, 3 H, CH_3), 3.89 (s, 3 H, CH_3), 5.28 (t, ^3J = 7.9 Hz, 1 H, 1-H), 6.68 (s, 1 H, 4′-H), 7.01 (t, ^3J = 7.9 Hz, 1 H, Ar*H*), 7.17 (t, ^3J = 7.9 Hz, 1 H, Ar*H*), 7.36 (d, ^3J = 7.9 Hz, 1 H, Ar*H*), 7.54 (d, ^3J = 7.9 Hz, 1 H, Ar*H*) ppm. Minor: ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 1.98–2.68 (m, 4 H, CH_2), 3.84 (s, 3 H, CH_3), 3.85 (s, 3 H, CH_3), 3.89 (s, 3 H, CH_3), 3.98 (s, 3 H, CH_3), 5.28 (t, ^3J = 6.1 Hz, 1 H, 7-H), 6.73 (s, 1 H, 5-H), 7.01 (t, ^3J = 7.9 Hz, 1 H, Ar*H*), 7.16 (t, ^3J = 7.9 Hz, 1 H, Ar*H*), 7.36 (d, ^3J = 7.9 Hz, 1 H, Ar*H*), 7.52 (d, ^3J = 7.9 Hz, 1 H, Ar*H*) ppm. ^{13}C NMR (101 MHz, CD_3OD, 25 °C) (major and minor conformers without assignment): δ = 29.94, 31.31, 32.01, 40.65, 41.72, 56.63, 60.68, 61.75, 67.16, 68.42, 109.18, 109.40, 109.87, 110.42, 119.92, 121.39, 122.18, 122.70, 122.95, 123.47, 127.41, 138.64, 139.24, 139.96, 142.06, 152.47, 152.83 ppm. IR (ATR): $\tilde{\nu}$ = 964, 1000, 1036, 1073, 1103, 1125, 1144, 1196, 1211, 1259, 1273, 1317, 1341, 1373, 1402, 1433, 1466, 1491, 1506, 1596, 1619, 1707, 1733, 2936, 3058, 3415 (strong) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 206 (16), 219 (13), 234 (22), 248 (17), 262 (16), 277 (19), 294 (29), 309 (17), 320 (16), 335 (28), 353 (100) [M]$^+$. HRMS (EI, 70 eV): *m*/*z* calcd. for $C_{21}H_{23}NO_4$ [M]$^+$ 353.1627; found 353.163.

1′,2′,3′-Trimethoxybenzo[5′,6′:5,4]-6,7-dihydro-1-oxo-1*H*-cyclohepta[2,3-*b*]-1′′-methyl-1*H*-indole Oxime (23): Compound **20** (50 mg, 0.142 mmol), NH_2OH·HCl (55 mg, 0.8 mmol) and pyridine (65 µL, 0.8 mmol) were dissolved in absolute EtOH (0.6 mL) under argon atmosphere. The reaction mixture was stirred at reflux temperatures for 24 h before brine (3 mL) and EtOAc (5 mL) were added. The organic layer was separated, aqueous layer extracted with EtOAc (2 × 5 mL), combined organic extracts dried with Na_2SO_4, and solvents removed under reduced pressure. After column chromatography on silica gel (eluent EtOAc/petroleum ether, 1:2) compound **23** (43 mg, 83%) was obtained as a yellow solid. R_f = 0.4 (EtOAc/petroleum ether, 2:3), m.p. 191 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.58–2.93 (m, 2 H, CH_2C=NOH), 2.98–3.28 (m, 2 H, CH_2Ar), 3.42 (s, 3 H, CH_3), 3.89 (s, 3 H, CH_3), 3.92 (s, 3 H, CH_3), 3.98 (s, 3 H, CH_3), 6.66 (s, 1 H, 4′-H), 7.10–7.22 (m, 1 H, Ar*H*), 7.27–7.44 (m, 2 H, Ar*H*), 7.75 (d, ^3J = 8.0 Hz, 1 H, Ar*H*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 30.8,

31.9, 35.3, 56.2, 60.5, 61.5, 108.0, 109.6, 114.0, 119.8, 119.9, 123.2, 123.3, 125.8, 131.5, 136.4, 138.2, 141.4, 152.0, 154.6 ppm. IR (ATR): $\tilde{\nu}$ = 942, 956, 974, 994, 1040, 1080, 1103, 1130, 1157, 1196, 1238, 1261, 1313, 1343, 1369, 1398, 1465, 1496, 1597, 1714, 1734, 2933, 3367 (strong) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 206 (6), 219 (9), 237 (8), 248 (8), 265 (13), 276 (10), 292 (10), 308 (18), 319 (10), 337 (10), 349 (73), 366 (100) $[M]^+$. HRMS (EI, 70 eV): *m*/*z* calcd. for $C_{21}H_{22}N_2O_4$ $[M]^+$ 366.1580; found 366.158.

1′,2′,3′-Trimethoxybenzo[5′,6′:6,5]-1-acetamido-2-methoxy-7-hydro-1*H*-cyclohepta[3,4-*b*]-1′′-methyl-1*H*-indole (*rac*-26): Compound **23** (150 mg, 0.410 mmol) was dissolved in anhydrous THF (3 mL) under argon atmosphere. The solution was cooled to 0 °C and $LiAlH_4$ (47 mg, 1.23 mmol) was added portionwise. The reaction mixture was stirred for 10 min at room temp. and then for 2 h at reflux temperatures. The resulting suspension was cooled to room temp., quenched by dropwise addition of water (1 mL) (caution: vigorous gas evolution) followed by addition of brine (10 mL) and methyl *tert*-butyl ether (MTBE; 10 mL). The organic phase was separated, aqueous phase extracted with MTBE (2× 5 mL), the combined organic extracts were dried with Na_2SO_4 and solvents were removed under reduced pressure. After column chromatography on silica gel (eluent CH_2Cl_2/MeOH, 10:1) the corresponding α-methoxyamine [70 mg, R_f = 0.33 (CH_2Cl_2/MeOH, 10:1)] was obtained. The product was dissolved in CH_2Cl_2 (1 mL) under an argon atmosphere, the solution was cooled to 0 °C and pyridine (45 μL, 0.56 mmol) and acetic anhydride (47 μL, 0.49 mmol) were sequentially added. The reaction mixture was stirred for 10 min at room temp. and then quenched by addition of EtOH (1 mL). After removal of all volatiles under reduced pressure the crude reaction mixture was subjected to column chromatography on silica gel (eluent EtOAc/MeOH, 15:1) to yield compound *rac*-**26** (73 mg, 42% from **23**) as a white solid. R_f = 0.38 (EtOAc/MeOH, 15:1), m.p. 172 °C. In ^1H NMR spectra (CD_3OD and [D_8]-THF) two conformers are observed in 7:1 ratio. The data below correspond to the major conformer. ^1H NMR (300 MHz, [D_8]THF, 25 °C): δ = 1.85 [s, 3 H, C(O)CH_3], 2.37–2.51 (m, 1 H, 7-H), 2.53–2.69 (m, 1 H, 7-H), 2.94 (s, 3 H, CH_3), 3.39 (s, 3 H, CH_3), 3.80 (s, 3 H, CH_3), 3.82 (s, 3 H, CH_3), 3.85 (s, 3 H, CH_3), 4.53–4.70 (m, 1 H, 1-H), 4.73 (s, 1 H, 2-H), 6.71 (s, 1 H, 4′-H), 7.01 (d, ^3J = 7.5 Hz, 1 H, Ar*H*), 7.09–7.23 (m, 2 H, Ar*H*, N*H*), 7.38 (d, ^3J = 7.5 Hz, 1 H, Ar*H*), 7.65 (d, ^3J = 7.5 Hz, 1 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, [D_8]THF, 25 °C): δ = 22.5, 29.6, 38.8, 55.3, 56.0, 60.2, 60.5, 60.8, 78.7, 109.5, 110.0, 111.6, 119.7, 121.9, 122.3, 123.1, 126.9, 133.1, 136.4, 138.1, 142.45, 151.9, 152.5, 168.6 ppm. IR (ATR): $\tilde{\nu}$ = 930, 956, 990, 1033, 1060, 1104, 1146, 1193, 1233, 1256, 1326, 1372, 1403, 1464, 1490, 1545, 1596, 1647, 2826, 2930, 3060, 3280 cm^{-1}. MS (ESI): *m*/*z* (%) = 204 (4), 334 (7), 365 (12), 393 (9), 413 (10), 447 (100) $[M + Na]^+$. HRMS (EI, 70 eV): *m*/*z* calcd. for $C_{24}H_{28}N_2O_5$ $[M]^+$ 424.1998; found 424.199.

1′,2′,3′-Trimethoxybenzo[5′,6′:5,4]-1-acetamido-6,7-dihydro-1*H*-cyclohepta[2,3-*b*]-1′′-methyl-1*H*-indole (*rac*-9): Oxime **23** (86 mg, 0.235 mmol) was dissolved in absolute MeOH (4.5 mL) under an argon atmosphere at 50 °C. The solution was then slowly cooled to room temp. and $NiCl_2$ (60 mg, 0.469 mmol) and $NaBH_4$ (53 mg, 1.410 mmol) were sequentially added (caution: vigorous hydrogen evolution). The reaction mixture was stirred at room temp. for 12 h, a new portion of $NiCl_2$ (60 mg, 0.469 mmol) and $NaBH_4$ (53 mg, 1.410 mmol) was added and the stirring was continued for further 12 h. The reaction mixture was then diluted with EtOAc (25 mL), the resulting suspension filtered through Celite® and the volatiles were removed under reduced pressure. After column chromatography on silica gel (eluent CH_2Cl_2/MeOH, 10:1) amine **24** (60 mg, 72%) was obtained as a white solid. R_f = 0.24 (CH_2Cl_2/MeOH, 10:1), m.p. 154 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.20–2.81 (m, 4 H, CH_2), 3.50 (s 3 H, CH_3), 3.45–4.00 (m, 2 H, NH_2), 3.79 (s, 3 H, CH_3), 3.91 (s, 3 H, CH_3), 3.96 (s, 3 H, CH_3), 4.49–4.63 (m, 1 H, 1-H), 6.66 (s, 1 H, 4′-H), 7.13 (t, ^3J = 7.9 Hz, 1 H, Ar*H*), 7.25 (t, ^3J = 7.9 Hz, 1 H, Ar*H*), 7.34 (d, ^3J = 7.9 Hz, 1 H, Ar*H*), 7.68 (d, ^3J = 7.9 Hz, 1 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 29.9, 32.0, 56.2, 60.5, 61.6, 108.5, 109.3, 119.7, 120.4, 121.9, 122.3, 126.3, 136.5, 137.0, 141.4, 151.6, 152.0 ppm. IR (ATR): $\tilde{\nu}$ = 916, 966, 993, 1006, 1043, 1100, 1143, 1193, 1234, 1311, 1343, 1404, 1456, 1490, 1570, 1594, 1733, 2840, 2930, 3353 (broad) cm^{-1}.

Amine **24** (60 mg, 0.17 mmol) was dissolved in CH_2Cl_2 (1 mL) under an argon atmosphere. The solution was cooled to 0 °C and pyridine (38 μL, 0.47 mmol) and acetic anhydride (29 μL, 0.31 mmol) were sequentially added. The reaction mixture was stirred for 10 min at 0 °C, quenched with EtOH (1 mL) followed by evaporation of the volatiles under reduced pressure. After column chromatography on silica gel (eluent EtOAc/MeOH, 15:1) product *rac*-**9** (57 mg, 85%) was obtained as a white solid. R_f = 0.5 (EtOAc/MeOH, 15:1), m.p. 178 °C. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.70 [s, 3 H, C(O)CH_3], 2.18–2.27 (m, 1 H, CH_2CNHAc), 2.48–2.54 (m, 1 H, CH_2CNHAc), 2.57–2.65 (m, 1 H, CH_2Ar), 2.68–2.76 (m, 1 H, CH_2Ar), 3.50 (s, 3 H, CH_3), 3.86 (s, 3 H, CH_3), 3.93 (s, 3 H, CH_3), 3.98 (s, 3 H, CH_3), 5.52 (td, ^3J = 8.4, ^4J = 2.2 Hz, 1 H, 1-H), 5.58 (d, ^3J = 8.4 Hz, 1 H, N*H*), 6.68 (s, 1 H, 4′-H), 7.13 (t, ^3J = 7.5 Hz, 1 H, Ar*H*), 7.24 (t, ^3J = 7.5 Hz, 1 H, Ar*H*), 7.36 (d, ^3J = 7.5 Hz, 1 H, Ar*H*), 7.66 (d, ^3J = 7.5 Hz, 1 H, Ar*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 23.2, 29.9, 31.9, 41.0, 43.8, 56.2, 60.3, 61.5, 108.4, 109.2, 109.4, 119.6, 120.9, 121.7, 122.1, 126.1, 136.6, 136.7, 138.3, 141.3, 151.6, 151.9, 168.6 ppm. IR (ATR): $\tilde{\nu}$ = 904, 928, 950, 977, 1031, 1040, 1078, 1103, 1122, 1144, 1195, 1232, 1257, 1308, 1336, 1371, 1400, 1465, 1487, 1536, 1628, 1649, 2826, 2930, 3040, 3220 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 191 (18), 206 (19), 218 (12), 234 (20), 248 (10), 262 (12), 277 (13), 291 (43), 309 (25), 320 (28), 336 (33), 351 (7), 379 (3), 394 (100) $[M]^+$. HRMS (EI, 70 eV): *m*/*z* calcd. for $C_{21}H_{23}N_2O_4$ $[M]^+$ 394.1892; found 394.189.

(*E*)-3-(2′-Iodo-3′,4′,5′-trimethoxyphenyl)-1-(1′′-{[2′′′-(trimethylsilyl)ethoxy]methyl}-1*H*-indol-2′′-yl)propen-2-one-1 (31): Ketone **29** (1.06 g, 3.46 mmol) and aldehyde **30** (1 g, 3.3 mmol) were dissolved in EtOH (50 mL) and 2 aqueous NaOH (10 mL) was slowly added to avoid precipitate formation. The reaction mixture was stirred for 12 h at room temp. before the solvent was removed under reduced pressure. To the residue EtOAc (100 mL) and water (20 mL) were added, the organic phase separated, and aqueous phase extracted with EtOAc (2× 50 mL). The combined organic layers were washed with brine (50 mL), dried with $MgSO_4$ and the solvent was removed under reduced pressure. After column chromatography on silica gel (eluent EtOAc/CyH, 1:6) compound **31** (1.91 g, 93%) was isolated as a bright-yellow viscous oil. R_f = 0.32 (EtOAc/Cy, 1:5). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = –0.08 [s, 9 H, Si(CH_3)$_3$], 0.90 (t, ^3J = 8.1 Hz, 2 H, CH_2Si), 3.59 (t, ^3J = 8.1 Hz, 2 H, CH$_2$CH_2O), 3.90 (s, 3 H, CH_3), 3.94 (s, 3 H, CH_3), 3.97 (s, 3 H, CH_3), 6.13 (s, 2 H, NCH_2O), 7.09 (s, 1 H, 3′′-H), 7.17–7.25 (m, 1 H, Ar*H*), 7.27 (d, $^3J_{trans}$ = 15.4 Hz, 1 H, 2-H), 7.38–7.46 (m, 1 H, Ar*H*), 7.47 (s, 1 H, 6′-H), 7.61 (d, ^3J = 8.4 Hz, 1 H, Ar*H*), 7.73 (d, ^3J = 8.0 Hz, 1 H, Ar*H*), 8.07 (d, $^3J_{trans}$ = 15.4 Hz, 1 H, 3-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = –1.3, 18.0, 56.5, 61.0, 61.3, 65.8, 73.5, 91.2, 106.7, 111.8, 114.0, 121.8, 123.0, 126.3, 126.5, 126.8, 134.1, 135.9, 140.8, 143.9, 146.8, 153.7, 154.0, 182.4 ppm. IR (ATR): $\tilde{\nu}$ = 923, 966, 1003, 1050, 1073, 1100, 1120, 1160, 1196, 1246, 1282, 1310, 1336, 1381, 1420, 1473, 1510, 1550, 1576, 1591, 1610, 1649 (strong), 2946 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 438 (92),

466 (35), 477 (16), 492 (100), 510 (8), 535 (13), 551 (10), 593 (5) $[M]^+$. HRMS (EI, 70 eV): *m*/*z* calcd. for $C_{26}H_{32}NO_5Si$ $[M - I]^+$ 466.2050; found 466.202.

3-(2′-Iodo-3′,4′,5′-trimethoxyphenyl)-1-(1′′-{[2′′′-(trimethylsilyl)-ethoxy]methyl}-1*H*-indol-2′′-yl)propanone-1 (32): Enone **31** (1.9 g, 3.2 mmol) was dissolved in degassed anhydrous C_6H_6 (80 mL) under an argon atmosphere and H_2O (58 μL, 3.2 mmol) and $[Ph_3PCuH]_6$ (1.74 g, 1 mmol) were sequentially added. The reaction mixture was stirred for 6 h at room temp. before the reaction flask was opened to ambient atmosphere and stirring was continued for a further 1 h. The resulting suspension was filtered through Celite® and the volatiles were removed under reduced pressure. After column chromatography on silica gel (eluent EtOAc/Cy, 1:4) compound **32** (1.83 g, 96%) was obtained as colorless viscous oil. R_f = 0.39 (EtOAc/Cy, 1:5). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = –0.07 [s, 9 H, Si(C*H*$_3$)$_3$], 0.89 (t, ^3J = 8.1 Hz, 2 H, C*H*$_2$Si), 3.12–3.23 [m, 2 H, C*H*$_2$C(O)], 3.24–3.34 (m, 2 H, C*H*$_2$Ar), 3.56 (t, ^3J = 8.1 Hz, 2 H, CH$_2$C*H*$_2$O), 3.84 (s, 3 H, C*H*$_3$), 3.85 (s, 3 H, C*H*$_3$), 3.89 (s, 3 H, C*H*$_3$), 6.05 (s, 2 H, NC*H*$_2$O), 6.75 (s, 1 H, 3′′-H), 7.13–7.23 (m, 1 H, Ar*H*), 7.34–7.44 (m, 1 H, 6′-H), 7.55 (d, ^3J = 8.3 Hz, 1 H, Ar*H*), 7.67 (d, ^3J = 7.9 Hz, 1 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = –1.3, 17.9, 36.3, 40.4, 56.2, 60.8, 61.0, 65.7, 73.3, 87.9, 109.3, 111.6, 113.8, 121.6, 123.0, 126.2, 126.6, 134.4, 139.5, 140.4, 140.6, 153.3, 153.7, 192.6 ppm. IR (ATR): $\tilde{\nu}$ = 920, 976, 1005, 1073, 1098, 1161, 1193, 1245, 1310, 1340, 1385, 1423, 1446, 1476, 1513, 1556, 1610, 1660 (strong), 2893, 2935 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 394 (14), 410 (76), 425 (11), 441 (8), 468 (100), 477 (9), 494 (4), 512 (4), 536 (1), 552 (1), 595 (5) $[M]^+$. HRMS (EI, 70 eV): *m*/*z* calcd. for $C_{26}H_{34}NO_5Si$ $[M - I]^+$ 468.2206; found 468.219.

1′,2′,3′-Trimethoxybenzo[5′,6′:5,4]-6,7-dihydro-1-oxo-1*H*-cyclohepta[2,3-*b*]-1′′-[2′′′-(trimethylsilyl)ethoxy]methyl-1*H*-indole (33): The reaction was carried out in a sealed microwave reactor vial (10 bar pressure limit). Compound **32** (400 mg, 0.67 mmol), $Pd_2(dba)_3$·$CHCl_3$ (69 mg, 0.067 mmol) and CsOC(O)*t*Bu (472 mg, 2.02 mmol) were dissolved in degassed anhydrous DMF (8 mL) under an argon atmosphere and the reaction vessel was sealed. The reaction mixture was stirred for 6 h at 90 °C, then cooled to room temp., diluted with EtOAc (50 mL), filtered through a pad of Celite® and concentrated under reduced pressure. After column chromatography on silica gel (eluent EtOAc/Cy, 1:4) an inseparable mixture of ketone **33** with the corresponding enone (260 mg, 83% of **33** based on GC-analysis, 68% yield) was isolated as a pale-yellow viscous oil. R_f = 0.32 (EtOAc/Cy, 1:4). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = –0.09 [s, 9 H, Si(C*H*$_3$)$_3$], 0.79–0.95 (m, 2 H, C*H*$_2$Si), 2.66–2.84 [m, 2 H, C*H*$_2$C(O)], 2.96–3.19 (m, 2 H, C*H*$_2$Ar), 3.36 (s, 3 H, C*H*$_3$), 3.46–3.68 (m, 2 H, CH$_2$C*H*$_2$O), 3.94 (s, 3 H, C*H*$_3$), 3.98 (s, 3 H, C*H*$_3$), 5.80 (d, ^2J = 10.7 Hz, 1 H, NC*H*$_2$O), 6.07 (d, ^2J = 10.7 Hz, 1 H, NC*H*$_2$O), 6.69 (s, 1 H, 4′-H), 7.14–7.22 (m, 1 H, Ar*H*), 7.36–7.44 (m, 1 H, Ar*H*), 7.57 (d, ^3J = 8.5 Hz, 1 H, Ar*H*), 7.76 (d, ^3J = 8.1 Hz, 1 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = –1.3, 18.0, 30.7, 46.8, 56.2, 60.9, 61.6, 66.0, 73.3, 107.5, 111.0, 118.5, 120.8, 121.0, 125.3, 125.6, 126.3, 132.6, 136.9, 139.3, 141.6, 152.8, 197.3 ppm. IR (ATR): $\tilde{\nu}$ = 910, 933, 993, 1033, 1073, 1096, 1125, 1153, 1170, 1193, 1243, 1310, 1344, 1396, 1460, 1493, 1594, 1649 (strong), 2846, 2893, 2947 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 191 (10), 207 (8), 220 (7), 236 (6), 248 (7), 262 (7), 277 (7), 292 (9), 308 (11), 320 (6), 335 (21), 350 (32), 366 (26), 378 (5), 394 (100), 437 (7), 467 (30) $[M]^+$. HRMS (EI, 70 eV): *m*/*z* calcd. for $C_{26}H_{33}NO_5Si$ $[M]^+$ 467.2128; found 467.213.

1′,2′,3′-Trimethoxybenzo[5′,6′:5,4]-6,7-dihydro-1-oxo-1*H*-cyclohepta[2,3-*b*]-1*H*-indole (34): 2 aqueous HCl (2 mL) was added at room temp. to a solution of **33** (200 mg, 0.43 mmol) in EtOH (8 mL) and the reaction mixture was stirred at 75 °C for 3 h. The resulting solution was neutralized with saturated aqueous $NaHCO_3$ and the organic solvent was removed under reduced pressure. The residue was extracted with EtOAc (3 × 15 mL), combined organic extracts washed with brine, dried with $MgSO_4$ and the solvent was removed under reduced pressure. Product **34** was then crystallized from hexane/EtOH to give a yellow polycrystalline powder (117 mg, 81%). R_f = 0.3 (EtOAc/Cy, 1:2), m.p. 188 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.69–3.14 (m, 4 H, C*H*$_2$), 3.38 (s, 3 H, C*H*$_3$), 3.94 (s, 3 H, C*H*$_3$), 4.00 (s, 3 H, C*H*$_3$), 6.70 (s, 1 H, 4′-H), 7.08–7.18 (m, 1 H, Ar*H*), 7.31–7.48 (m, 2 H, Ar*H*), 7.86 (d, ^3J = 8.3 Hz, 1 H, Ar*H*), 9.23 (s, 1 H, N*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 31.0, 43.6, 56.2, 60.9, 61.6, 108.1, 111.7, 119.0, 120.3, 126.1, 126.3, 126.5, 131.7, 136.7, 136.8, 141.8, 152.6, 152.7, 195.2 ppm. IR (ATR): $\tilde{\nu}$ = 904, 996, 1043, 1076, 1106, 1140, 1190, 1236, 1256, 1310, 1333, 1348, 1376, 1396, 1460, 1488, 1516, 1590, 1633 (strong), 2846, 2933, 3313 (strong) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 208 (35), 220 (9), 236 (25), 251 (5), 262 (7), 279 (16), 294 (35), 308 (15), 322 (7), 337 (100) $[M]^+$. HRMS (EI, 70 eV): *m*/*z* calcd. for $C_{20}H_{19}NO_4$ $[M]^+$ 337.1314; found 337.131.

1′,2′,3′-Trimethoxybenzo[5′,6′:5,4]-6,7-dihydro-1-hydroxy-1*H*-cyclohepta[2,3-*b*]-1*H*-indole (*rac*-35): $NaBH_4$ (8 mg, 0.21 mmol) was added to a solution of **34** (70 mg, 0.21 mmol) in MeOH/THF (3 mL, 1:2 vol. ratio) and the reaction mixture was stirred at room temp. for 1 h. The resulting solution was diluted with brine (10 mL) and MTBE (20 mL), the organic phase separated, the aqueous phase extracted with MTBE (2 × 10 mL), and the combined organic extracts dried with $MgSO_4$. After column chromatography on silica gel (eluent EtOAc/Cy, 1:1) compound *rac*-**35** (70 mg, 97%) was obtained as a white polycrystalline powder. R_f = 0.3 (EtOAc/Cy, 1:1), m.p. 174 °C. In ^{1}H NMR spectra (CD_3OD) two conformers are observed in about 7:1 ratio. The data below correspond to the major conformer. ^{1}H NMR (500 MHz, CD_3OD, 25 °C): δ = 2.13–2.23 (m, 1 H, C*H*$_2$COH), 2.39–2.55 (m, 2 H, C*H*$_2$Ar), 2.59–2.70 (m, 1 H, C*H*$_2$COH), 3.39 (s, 3 H, OC*H*$_3$), 3.86 (s, 3 H, OC*H*$_3$), 3.89 (s, 3 H, OC*H*$_3$), 4.78–4.90 (m, 1 H, 1-H), 6.76 (s, 1 H, 4′-H), 7.00 (t, ^3J = 7.5 Hz, 1 H, Ar*H*), 7.07 (t, ^3J = 7.5 Hz, 1 H, Ar*H*), 7.42 (d, ^3J = 7.5 Hz, 1 H, Ar*H*), 7.56 (d, ^3J = 7.5 Hz, 1 H, Ar*H*) ppm. ^{13}C NMR (126 MHz, CD_3OD, 25 °C): δ = 32.2, 44.5, 56.6, 60.5, 61.7, 67.3, 106.9, 110.0, 112.1, 119.9, 121.4, 122.1, 123.0, 128.2, 136.7, 137.9, 141.0, 142.0, 152.2, 152.4 ppm. IR (ATR): $\tilde{\nu}$ = 924, 976, 1000, 1039, 1056, 1092, 1110, 1129, 1192, 1234, 1254, 1308, 1334, 1402, 1454, 1490, 1592, 2487 (broad), 2849, 2930, 3390 (broad) cm^{-1}. HRMS (ESI, 70 eV): *m*/*z* calcd. for $C_{20}H_{21}NO_4Na$ $[M + Na]^+$ 362.1363; found 362.1361: calcd. for $C_{20}H_{19}NO_3Na$ $[M - H_2O + Na]^+$ 344.1257; found 344.1254.

3-(2′-Iodo-3′,4′,5′-trimethoxyphenyl)propionic Acid (36): 3-(3′,4′,5′-Trimethoxyphenyl)propionic acid **13** (7 g, 29 mmol) was dissolved in CH_2Cl_2 (20 mL) and silver trifluoroacetate (6.85 g, 34 mmol) was added upon stirring. A solution of iodine (7.87 g, 34 mmol) in CH_2Cl_2 (160 mL) was added dropwise over 6 h at room temp. and the reaction mixture was stirred for a further 1 h followed by filtration through Celite®. The filtrate was washed with saturated aq. $Na_2S_2O_3$ (50 mL), water (50 mL), saturated aq. $NaHCO_3$ (50 mL), brine, dried with $MgSO_4$, and the solvent was removed under reduced pressure. After crystallization from petroleum ether/EtOAc (1:1 vol. ratio) compound **36** (9.85 g, 92%) was obtained as a white polycrystalline solid. R_f = 0.3 (petroleum ether/EtOAc, 1:1), m.p. 110 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.69 (t, ^3J = 7.8 Hz, 2 H, C*H*$_2$), 3.06 (t, ^3J = 7.8 Hz, 2 H, C*H*$_2$), 3.84 (s, 3 H, OC*H*$_3$), 3.85 (s, 3 H, OC*H*$_3$), 3.87 (s, 3 H, OC*H*$_3$), 6.70 (s, 1 H, Ar*H*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 34.1, 35.8,

6.1, 60.7, 60.9, 87.9, 109.1, 138.3, 140.7, 140.7, 153.7, 153.1, 178.0 ppm. $C_{12}H_{15}IO_5$ (366.15): calcd. C 39.36, H 4.13; found C 39.42, H 4.14.

1-(1*H*-Benzo[*d*][1′,2′,3′]triazol-1′-yl)-3-(2′′-iodo-3′′,4′′,5′′-trimethoxyphenyl)propan-1-one (38): 1-methylsulfonyl-1*H*-benzotriazole (0.364 g, 1.85 mmol) and triethylamine (0.36 mL, 2.6 mmol) were added to a solution of acid **36** (0.68 g, 1.85 mmol) in THF (10 mL) and the reaction mixture was stirred at 65 °C for 24 h. After evaporation of all volatiles under reduced pressure the product was isolated by using column chromatography on silica gel (eluent petroleum ether/EtOAc, 2:1) to give compound **38** (67 mg, 70%) as a white solid. R_f = 0.55 (petroleum ether/EtOAc, 1:1), m.p. 86 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.31–3.35 (t, ^3J = 7.7 Hz, 2 H, ArCH_2), 3.72–3.77 [t, ^3J = 7.7 Hz, 2 H, CH_2C(O)], 3.83 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 6.78 (s, 1 H, 6′-H), 7.51 (t, ^3J = 7.7 Hz, 1 H, 3-H), 7.67 (t, ^3J = 7.7 Hz, 1 H, 2-H), 8.12 (d, ^3J = 8.3 Hz, 1 H, 4-H), 8.30 (d, ^3J = 8.3 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 35.6, 36.1, 56.3, 60.9, 61.1, 88.1, 109.3, 114.4, 120.3, 126.3, 130.6, 131.1, 138.2, 140.9, 146.3, 153.4, 153.8, 171.4 ppm. IR (ATR): $\tilde{\nu}$ = 751, 771, 782, 924, 959, 1004, 1034, 1074, 1104, 1166, 1199, 1238, 1288, 1327, 1387 (strong), 1450, 1482, 1564, 1737 (strong), 2847, 2937, 2966 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 165 (33), 179 (27), 193 (20), 207 (60), 221 (19), 237 (10), 251 (12), 254 (18), 266 (60), 282 (37), 291 (13), 307 (48), 312 (30), 320 (100), 467 (80) [M]$^+$. $C_{18}H_{18}IN_3O_4$ (467.26): calcd. C 46.27, H 3.88, N 8.99; found C 46.21, H 3.87, N 9.02.

3-(2′-Iodo-3′,4′,5′-trimethoxyphenyl)-1-(1′′-methyl-1*H*-indol-3′′-yl)propan-1-one (12): Titanium tetrachloride (215 µL, 2.0 mmol) was added to a solution of **38** (482 mg, 1.0 mmol) and 1-methyl-1*H*-indole (158 µL, 1.25 mmol) in CH_2Cl_2 (10 mL) under an argon atmosphere. The reaction mixture was stirred for 4 h at room temp. followed by quenching with MeOH (1 mL) and evaporation of the solvent under reduced pressure. After column chromatography on silica gel (eluent petroleum ether/EtOAc, 1:1) compound **12** (239 mg, 50%) was obtained as a white polycrystalline powder. R_f = 0.49 (petroleum ether/EtOAc, 1:1), m.p. 153 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.10–3.16 [m, 2 H, CH_2C(O)], 3.18–3.25 (m, 2 H, CH_2Ar), 3.79 (s, 3 H, NCH_3), 3.82 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 6.76 (s, 1 H, 6′-H), 7.29–7.35 (m, 3 H, 5′′-H, 6′′-H, 7′′-H), 7.75 (s, 1 H, 2′′-H), 8.38–8.44 (m, 1 H, 4′′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 33.7, 36.6, 40.3, 56.3, 60.9, 61.1, 87.8, 109.5, 109.7, 116.6, 122.7, 122.8, 123.5, 126.4, 135.7, 137.6, 140.2, 140.5, 153.2, 153.7, 194.2 ppm. IR (ATR): $\tilde{\nu}$ = 747, 925, 1007, 1089, 1103, 1126, 1164, 1200, 1249, 1271, 1328, 1337, 1374, 1387, 1425, 1464, 1479, 1530, 1560, 1577, 1642, 2849, 2918, 2958, 3380 (strong) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 158 (51), 352 (100), 479 (1) [M]$^+$. $C_{21}H_{22}INO_4$ (479.31): calcd. C 52.62, H 4.63, N 2.92; found C 52.69, H 4.64, N 2.92.

1′,2′,3′-Trimethoxybenzo[5′,6′:5,4]-6,7-dihydro-1-oxo-1*H*-cyclohepta-[3,2-*b*]-1′′-methyl-1*H*-indole (39): The reaction was carried out in a glass vial (10 bar pressure limit) equipped with a mininert® Teflon® valve. Compound **12** (100 mg, 0.209 mmol), $Pd(OAc)_2$ (4.7 mg, 0.02 mmol), pivalic acid (53 mg, 0.523 mmol) and Cs_2CO_3 (204 mg, 0.627 mmol) were dissolved in anhydrous degassed DMF (2 mL) under an argon atmosphere and the reaction mixture was stirred at 110 °C for 24 h. The resulting suspension was cooled to room temp., diluted with EtOAc (20 mL), and filtered through Celite® before evaporation of all volatiles under reduced pressure. After column chromatography on silica gel (eluent petroleum ether/EtOAc, 3:2) compound **39** (53 mg, 76%) was obtained as a pale-yellow solid. R_f = 0.41 (petroleum ether/EtOAc, 1:1), m.p. 172 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.59–2.82 [m, 2 H, CH_2C(O)], 2.94–3.22 (m, 2 H, CH_2Ar), 3.45 (s, 3 H, CH_3), 3.70 (s, 3 H, CH_3), 3.95 (s, 3 H, CH_3), 3.96 (s, 3 H, CH_3), 6.72 (s, 1 H, 4′-H), 7.29–7.48 (m, 3 H, 5′′-H, 6′′-H, 7′′-H), 8.38 (m, 1 H, 4′′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 31.4, 33.2, 45.6, 56.3, 61.3, 61.5, 108.0, 109.9, 114.7, 115.4, 122.2, 122.9, 123.6, 126.5, 138.0, 139.0, 141.4, 152.7, 154.5, 198.4 ppm. IR (ATR): $\tilde{\nu}$ = 750, 920, 1017, 1087, 1126, 1195, 1233, 1316, 1340, 1394, 1461, 1490, 1493, 1594, 1627, 1632, 2851, 2935 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 139 (9), 146 (12), 175 (9), 193 (10), 205 (28), 222 (9), 248 (12), 276 (9), 292 (9), 308 (18), 320 (60), 351 (100) [M]$^+$. $C_{21}H_{21}NO_4$ (351.40): calcd. C 71.78, H 6.02, N 3.99; found C 71.93, H 6.04, N 3.98.

1′,2′,3′-Trimethoxybenzo[5′,6′:5,4]-6,7-dihydro-1-oxo-1*H*-cyclohepta[3,2-*b*]-1′′-methyl-1*H*-indole Oxime (40): Ketone **39** (130 mg, 0.37 mmol), $NH_2OH{\cdot}HCl$ (142 mg, 2.04 mmol) and pyridine (164 µL, 2.04 mmol) were dissolved in absolute EtOH (1.85 mL) under an argon atmosphere. The reaction mixture was stirred at reflux temperatures for 24 h before brine (3 mL) and EtOAc (5 mL) were added. The organic layer was separated, aqueous layer extracted with EtOAc (2× 5 mL), combined organic extracts were dried with Na_2SO_4 and all solvents were removed under reduced pressure. After column chromatography on silica gel (eluent petroleum ether/EtOAc/EtOH, 3:1:0.05) compound **40** (113 mg, 83%) was obtained as a yellow solid. R_f = 0.5 (EtOAc/petroleum ether, 1:1), m.p. 185 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.05 (s, 1 H, OH), 2.62–2.75 (m, 1 H, CH_2), 2.81–2.94 (m, 2 H, CH_2), 3.26–3.40 (m, 1 H, CH_2), 3.45 (s, 3 H, CH_3), 3.68 (s, 3 H, CH_3), 3.93 (s, 6 H, CH_3), 6.69 (s, 1 H, 4′-H), 7.20–7.25 (m, 1 H, Ar*H*), 7.28–7.34 (m, 1 H, Ar*H*), 7.41 (d, ^3J = 8.1 Hz, 1 H, 7′′-H), 8.05 (d, ^3J = 7.7 Hz, 1 H, 4′′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 31.1, 32.4, 34.4, 56.3, 61.0, 61.6, 108.2, 109.7, 110.2, 116.4, 120.8, 121.0, 122.6, 125.8, 136.1, 137.9, 138.4, 141.2, 151.9, 153.8, 157.0 ppm. IR (ATR): $\tilde{\nu}$ = 742, 909, 977, 981, 1017, 1095, 1196, 1313, 1320, 1392, 1425, 1456, 1464, 1490, 1559, 1592, 1599, 1739, 2843, 2934, 3450 cm^{-1}. **MS** (EI, 70 eV): *m*/*z* (%) = 183 (7), 319 (14), 349 (13), 366 (100) [M]$^+$. $C_{21}H_{22}N_2O_4$ (366.41): calcd. C 68.84, H 6.05, N 7.65; found C 69.02, H 6.07, N 7.63.

1′,2′,3′-Trimethoxybenzo[5′,6′:5,4]-1-acetamido-6,7-dihydro-1*H*-cyclohepta[3,2-*b*]-1′′-methyl-1*H*-indole (*rac*-10): Oxime **40** (107 mg, 0.292 mmol) was dissolved in absolute MeOH (5 mL) under an argon atmosphere at 50 °C. The solution was then slowly cooled to room temp. and $NiCl_2$ (75 mg, 0.585 mmol) and $NaBH_4$ (66 mg, 1.752 mmol) were sequentially added (caution: vigorous hydrogen evolution). The reaction mixture was stirred at room temp. for 12 h and a new portion of $NiCl_2$ (38 mg, 0.292 mmol) and $NaBH_4$ (11 mg, 0.292 mmol) was added after each 2 h. The reaction mixture was then diluted with EtOAc (20 mL), the resulting suspension filtered through Celite® and the volatiles were removed under reduced pressure. After column chromatography on silica gel (eluent EtOAc/EtOH/Et_3N, 10:1:0.2) the corresponding amine (41 mg, 40%) was obtained as a pale-brown solid. R_f = 0.25 (EtOAc/EtOH/Et_3N, 10:1:0.2). ^{1}H NMR (400 MHz, CD_3OD, 25 °C) (ca. 1:1 mixture of conformers): δ = 1.96–2.06 (m, 1 H, CH_2), 2.07–2.16 (m, 1 H, CH_2), 2.22–2.32 (m, 1 H, CH_2), 2.41–2.58 (m, 4 H, CH_2), 2.59–2.68 (m, 1 H, CH_2), 3.46 (s, 3 H, CH_3), 3.52 (s, 3 H, CH_3), 3.61 (s, 3 H, CH_3), 3.62 (s, 3 H, CH_3), 3.87–3.93 (m, 1 H, 1-H), 3.87 (s, 3 H, CH_3), 3.88 (s, 3 H, CH_3), 3.89 (s, 3 H, CH_3), 3.90 (s, 3 H, CH_3), 4.53 (dd, ^3J = 8.3, ^3J = 2.2 Hz, 1 H, 1-H), 6.83 (s, 1 H, Ar*H*), 6.87 (s, 1 H, Ar*H*), 7.01–7.10 (m, 2 H, Ar*H*), 7.12–7.20 (m, 2 H, Ar*H*), 7.35–7.40 (m, 2 H, Ar*H*), 7.58 (d, ^3J = 7.9 Hz, 1 H, Ar*H*), 7.95 (d, ^3J = 8.1 Hz, 1 H, Ar*H*) ppm. ^{13}C NMR (400 MHz, CD_3OD, 25 °C) (ca. 1:1 mixture of conformers): δ = 31.8, 31.9, 32.7, 33.2, 43.9,

45.5, 46.1, 50.9, 56.6, 56.6, 60.8, 60.9, 61.7, 68.8, 109.8, 110.0, 110.5, 110.5, 115.8, 117.9, 118.2, 118.8, 118.9, 120.0, 120.4, 120.7, 121.9, 122.6, 126.5, 127.7, 133.3, 133.8, 138.7, 139.0, 139.6, 140.2, 141.9, 142.2, 152.2, 152.5, 154.8, 155.1 ppm. IR (ATR): $\tilde{\nu}$ = 741, 837, 877, 937, 975, 1013, 1107, 1118, 1196, 1229, 1398, 1452, 1463, 1487, 1491, 1590, 1594, 1597, 1653, 2859, 2935, 3358 cm^{-1}. The resulting amine (41 mg, 0.116 mmol) was then dissolved in anhydrous CH_2Cl_2 (0.5 mL) under an argon atmosphere, the resulting solution was cooled to 0 °C and pyridine (167 μL, 0.696 mmol) and acetyl chloride (25 μL, 0.348 mmol) were sequentially added. The reaction mixture was stirred for 10 min, quenched by addition of EtOH (1 mL) and the solvents were removed under reduced pressure. After column chromatography on silica gel (eluent EtOAc/EtOH, 98:2) compound *rac*-**10** (40.5 mg, 88%) was obtained as a white solid. R_f = 0.4 (EtOAc/EtOH, 98:2), m.p. 211 °C. ^{1}H NMR (400 MHz, CD_3OD, 25 °C) (mixture of conformers in about 1:1.75 ratio, with assignment if possible): δ = 1.77 [s, 1 H, C(O)CH_3, minor], 2.07 [s, 1 H, C(O)CH_3, major], 1.85–1.95 (m, 1 H, CH_2, minor), 2.16–2.25 (m, 1 H, CH_2, major), 2.30–2.41 (m, 2 H, CH_2, major), 2.53–2.63 (m, 2 H, CH_2, both), 2.64–2.74 (m, 1 H, CH_2, minor), 3.50 (s, 3 H, CH_3, major), 3.54 (s, 3 H, CH_3, minor), 3.60 (s, 3 H, CH_3, minor), 3.64 (s, 3 H, CH_3, major), 3.89 (s, 6 H, CH_3), 3.91 (s, 3 H, CH_3), 3.92 (s, 3 H, CH_3), 4.90 (dd, ^3J = 11.5, ^3J = 6.5 Hz, 1 H, 1-H, major), 5.61 (dd, ^3J = 9.0, ^3J = 5.8 Hz, 1 H, 1-H, minor), 6.83 (3, 1 H, 4′-H, minor), 6.86 (3, 1 H, 4′-H, major), 7.00–7.10 (m, 2 H, Ar*H*, both), 7.12–7.22 (m, 2 H, Ar*H*, both), 7.37 (d, ^3J = 7.9 Hz, 1 H, Ar*H*, minor), 7.39 (d, ^3J = 8.1 Hz, 1 H, Ar*H*, major), 7.61 (d, ^3J = 7.9 Hz, 1 H, Ar*H*, minor), 7.73 (d, ^3J = 8.1 Hz, 1 H, Ar*H*, major) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 °C) (mixture of conformers without assignment): δ = 22.5, 22.6, 31.8, 32.2, 32.3, 32.8, 39.5, 41.8, 45.7, 48.0, 56.6, 56.6, 61.0, 61.1, 61.7, 61.7, 109.6, 109.9, 110.4, 110.6, 113.6, 114.6, 117.8, 118.8, 119.1, 119.7, 120.1, 120.5, 122.0, 122.9, 126.4, 128.7, 133.6, 134.5, 139.0, 139.1, 139.2, 141.1, 142.0, 142.1, 152.4, 153.0, 154.9, 154.9, 171.8, 172.6 ppm. IR (ATR): $\tilde{\nu}$ = 757, 904, 1009, 1013, 1045, 1098, 1119, 1146, 1197, 1231, 1318, 1334, 1373, 1397, 1426, 1465, 1492, 1541, 1597, 1644, 1648, 2939, 3290 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 206 (8), 305 (10), 320 (24), 336 (100), 351 (10), 394 (84) $[M]^+$. $C_{23}H_{26}N_2O_4$ (394.46): calcd. C 70.03, H 6.64, N 7.10; found C 69.82, H 6.66, N 7.07.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of target compounds and synthetic intermediates, and detailed experimental procedures for the biological investigations.

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