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Synthesis of cytochalasan analogues with aryl substituents at position 10†

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Cytochalasans are fungal metabolites that are known to inhibit actin polymerization. Despite their remarkable bioactivity, there are few studies on the structure–activity relationship (SAR) of the cytochalasan scaffold. The full potential of structural modifications remains largely unexplored. The substituent at position 10 of the cytochalasan scaffold is derived from an amino acid incorporated into the cytochalasan core, thus limiting the structural variability at this position in natural products. Additionally, modifications at this position have only been achieved through semisynthetic or mutasynthetic approaches using modified amino acids. This paper introduces a modular approach for late-stage modifications at position 10 of the cytochalasan scaffold. Iron-mediated cross-coupling reactions with corresponding Grignard reagents were used to introduce aryl or benzyl groups in position 10, resulting in the synthesis of six new cytochalasan analogues bearing non-natural aromatic residues. This methodology enables further exploration of modifications at this position and SAR studies among cytochalasan analogues.

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Introduction

Cytochalasans are an important class of natural compounds that affect the dynamics of the actin cytoskeleton.^{1–3} They bind specifically the barbed end of F-actin, thus inhibiting the actin polymerization.^{4,5} As a result, cytochalasans exhibit cytotoxic effects and/or migrastatic activities by inhibiting cancer cell migration.^{6–9} The concept of migrastatics,^{10–12} *i.e.*, drugs that inhibit cancer cell invasion and metastasis, shows potential in developing new cancer therapies. Existing anticancer agents often fail to inhibit metastasis formation, which is a major contributor to cancer-related deaths.^{13,14} Therefore, cytochalasans and their analogues are promising candidates for medicinal chemists seeking to address this critical aspect of cancer treatment. At the same time, knowledge of the structure–activity relationship (SAR) of this class of compounds is limited^{15–21} and the full potential of structural modification has not been explored, yet.

Cytochalasans are hybrid fungal metabolites that combine polyketides and amino acids.²² They exhibit a characteristic structure consisting of a perhydroisoindolone core and a complex macrocycle. Cytochalasans can be classified based on the specific amino acid incorporated into the perhydroisoindolone core, which may include aromatic amino acids such as phenylalanine in cytochalasins (*e.g.*, cytochalasin B, **1**), tryptophan in chaetoglobosins (*e.g.*, chaetoglobosin A, **2**), *O*-methyltyrosine in pyrichalasin (*e.g.*, pyrichalasin H, **3**), and aliphatic amino acids such as leucine in aspochalasins, valine in trichalasin, and alanine inalachalasin (Fig. 1). Consequently, the cytochalasan scaffold exhibits limited structural variability in position 10 among natural cytochalasans. So far, analogues with modifications at position 10 have only been provided through a semisynthetic and mutasynthetic approach using non-natural amino acids, particularly substituted *L*-phenylalanines and *L*-tyrosines.^{23,24} Hence, there is untapped potential for further structural modifications at position 10 and investigations into the structure–activity relationship of cytochalasans.

Since their discovery, chemists have been pursuing the total synthesis of cytochalasans due to their intricate structure, which poses a persistent challenge.^{25–29} However, none of the total syntheses have involved the late-stage introduction of substituents into position 10, so far. Only a synthesis of cytochalasan analogues based on desymmetrization reactions of succinimide derivatives has been reported.¹⁸ Early attempts to introduce phenyl groups into the cytochalasan scaffold through cuprate reagents in the 1990s were unsuccessful.^{30,31}

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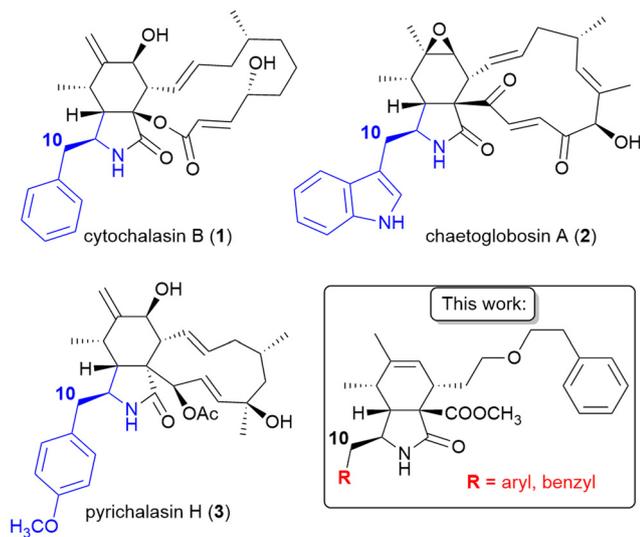


Fig. 1 Structures of natural cytochalasins with aromatic substituents in position 10 and cytochalasin analogues from this work. Amino acids incorporated into the cytochalasin core are shown in blue.

To date, all syntheses of cytochalasins have relied on the use of amino acids as starting materials. However, this approach is impractical for achieving modification at position 10, as each multistep synthesis would need to be optimized according to the amino acid being used. Therefore, a modular approach for introducing modifications to position 10 is necessary.

Although the first attempts for arylation in position 10 were unsuccessful thirty years ago, significant advancements have been made in synthetic methodology for sp^2 - sp^3 C-C bond formation. The transition metal-catalyzed couplings predominantly encompass arylations catalyzed by palladium,³² nickel,³³ cobalt,^{34,35} or iron.^{35,36} In this study, we investigated these reactions to achieve a modular approach for introducing aryl groups of different bulkiness in position 10 of the cytochalasin core. This approach facilitates the synthesis of derivatives modified at this position and enables more thorough SAR studies for cytochalasin analogues.

Results and discussion

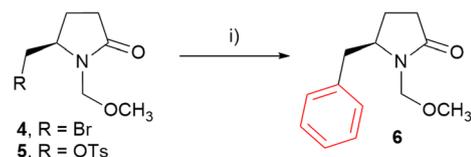
Our investigation aimed to develop a streamlined method for introducing aryl groups at position 10 of the cytochalasin core. Due to the complexity of the cytochalasin core, the arylation conditions were first screened using simple model compounds, specifically derivatives of 4-methyl-2-pyrrolidone. A transition-metal-catalyzed approach was chosen, such as Suzuki cross-coupling reactions with organoboron reagents,³⁷ or copper(I)-³⁸ and palladium(II)-mediated³⁹ reactions with corresponding Grignard reagents. However, none of these conditions provided the arylation. Consequently, our attention shifted towards cobalt(III)-⁴⁰ and iron(III)-catalyzed⁴¹ reactions.

The 2-pyrrolidone ring contains an amide group with an acidic hydrogen, susceptible to interaction with a base, such

as a Grignard reagent. Therefore, the consideration of an *N*-protecting group, such as benzoyl (Bz), *tert*-butyloxycarbonyl (Boc), or methoxymethyl (MOM) was paramount. In the cytochalasin synthesis, the *N*-benzoyl group is commonly employed, however, its instability under basic reaction conditions⁴² precludes its use in this approach. The Boc group, previously used in arylations of pyrrolidines,⁴⁰ is also unsuitable due to its propensity to enhance the electrophilicity of the 2-pyrrolidone carbonyl group, leading to lactam ring opening upon treatment with a strong nucleophile (data not shown). Thus, the MOM group was identified as the most appropriate choice, mitigating both of the issues.

The initial optimization step involved the selection of an appropriate leaving group for arylations. Bromide **4** and tosylate **5** were synthesized using established procedures or in analogy with known procedures.^{30,43–45} (see ESI for details, Scheme S1†). The reactions of the MOM-protected 4-methyl-2-pyrrolidone derivatives with phenylmagnesium bromide in the presence of $\text{Co}(\text{acac})_3$ (0.05 eq.) as a catalyst and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) as a ligand were carried out in THF at room temperature under an argon atmosphere (Scheme 1). In the case of tosylate **5**, arylation product **6** was not observed at all. Instead, bromide **4** provided the arylation in 5 h (entry 2, Table 1). Full conversion was achieved after 24 h and phenyl derivative **6** was isolated in 88% yield (entry 3, Table 1), indicating that bromine is a good leaving group for arylations.

Encouraged by the results, our interest extended to exploring the applicability of the reaction conditions to the arylations of unprotected 4-bromomethyl-2-pyrrolidone (**7**) (Scheme 2 and Table 2). In light of the anticipated interaction between the free NH group and the Grignard reagent, the quantity of phenylmagnesium bromide was elevated to 2.6 equivalents (Table 2, entry 1). The arylated pyrrolidone **8** was formed but full conversion was not achieved after 24 h. The formation of 4-methyl-2-pyrrolidone **9**, a debrominated byproduct, was also observed, likely due to a radical mechanism of the reaction. A reduction in the amount of TMEDA to a 1:1 ratio with the catalyst increased conversion and improved the ratio of phenyl derivative **8** to debrominated byproduct **9** (entry 2, Table 2). Further improvements in conversion and selectivity were achieved by elevating the reaction temperature to 55 °C (entry 3, Table 2). On the other hand, *in situ* protection of the amide group with *N,O*-bis(trimethylsilyl)acetamide (BSA)⁴⁶ only led to poor conversion (entry 4, Table 2). Replacement of the catalyst



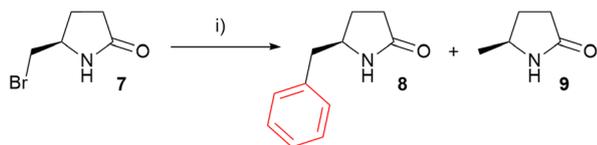
Scheme 1 Leaving group optimization for arylations of starting materials with 2-pyrrolidone moiety. Reagents and conditions: (i) PhMgBr (1.3 eq.), $\text{Co}(\text{acac})_3$ (0.05 eq.), TMEDA, THF, RT, see Table 1.



Table 1 Leaving group optimization for arylations of starting materials with 2-pyrrolidone moiety

Entry	Starting compd	R	TMEDA (eq.)	Time	Product	NMR ratio starting compd : product
1	5	OTs	0.14	24 h	4	62 : 38
2	4	Br	0.24	5 h	6	38 : 62 ^a
3	4	Br	0.24	24 h	6	0 : 100 ^b

^a Isolated yield 40%. ^b Isolated yield 88%.

**Scheme 2** Optimization of the cross-coupling reaction using unprotected pyrrolidone-type bromide 7. Reagents and conditions: (i) PhMgBr, catalyst, TMEDA, THF, see Table 2.

by Co(PPh₃)Cl₂ provided better or equal conversion compared to Co(acac)₃ but with a preference for the formation of debrominated byproduct 9 (entries 5 and 6, Table 2).

Due to unsatisfactory results with cobalt catalysts, Fe(acac)₃ was explored as a catalyst^{41,47} (Scheme 2 and Table 2). In these

experiments, the solvent was carefully degassed and the Grignard reagent was added at 0 °C. The full conversion was not achieved after 4.5 or 24 h, however, the debrominated byproduct 9 was not observed (entries 7 and 8, Table 2). Increasing the equivalents of the Grignard reagent resulted in an increased conversion, however, the debrominated byproduct 9 was also detected by ¹H NMR. In this case, the NMR ratio of the phenyl derivative 8 and debrominated byproduct 9 could not be accurately determined due to overlapping peaks (entry 9, Table 2). The reaction was also carried out using stoichiometric amounts of both Fe(acac)₃ and TMEDA in degassed or undegassed THF. In both cases, full conversion was achieved without the formation of debrominated byproduct 9. However, the isolated yield of the phenylated product 8 was higher when using degassed solvent (entries 10 and 11,

Table 2 Optimization of the cross-coupling reaction using pyrrolidone-type starting material

Entry	PhMgBr (eq.)	Catalyst (equivalents)	TMEDA (eq.)	Temperature	Time	NMR ratio 7 : 8 : 9
1	2.6	Co(acac) ₃ (0.05)	0.20	RT	24 h	49 : 18 ^a : 33
2	2.6	Co(acac) ₃ (0.05)	0.05	RT	24 h	30 : 41 : 29
3	2.6	Co(acac) ₃ (0.05)	0.05	55 °C	24 h	17 : 63 : 20
4 ^b	2.6	Co(acac) ₃ (0.05)	0.05	RT	18 h	92 : 8 : 0
5	2.6	Co(PPh ₃) ₂ Cl ₂ (0.05)	0.05	RT	48 h	21 : 35 : 44
6	2.6	Co(PPh ₃) ₂ Cl ₂ (0.05)	0.05	55 °C	24 h	19 : 38 : 43
7 ^c	2.6	Fe(acac) ₃ (0.05)	0.05	0 °C to RT	4.5 h	88 : 12 : 0
8 ^c	2.6	Fe(acac) ₃ (0.05)	0.05	0 °C to RT	24 h	83 : 17 : 0
9 ^c	7.7	Fe(acac) ₃ (0.05)	0.05	0 °C to RT	24 h	nd ^d
10	7.7	Fe(acac) ₃ (1.00)	1.00	0 °C to RT	18 h	0 : 100 ^e : 0
11 ^c	7.7	Fe(acac) ₃ (1.00)	1.00	0 °C to RT	18 h	0 : 100 ^f : 0

^a Isolated yield 13%. ^b (1) BSA, THF, 50 °C, 3 h (2) PhMgBr, catalyst, TMEDA, THF. ^c Degassed THF. ^d Compound 9 observed in ¹H NMR, ratio could not be determined, ratio 7 : 8 is 40 : 60. ^e Isolated yield 36%. ^f Isolated yield 59%.

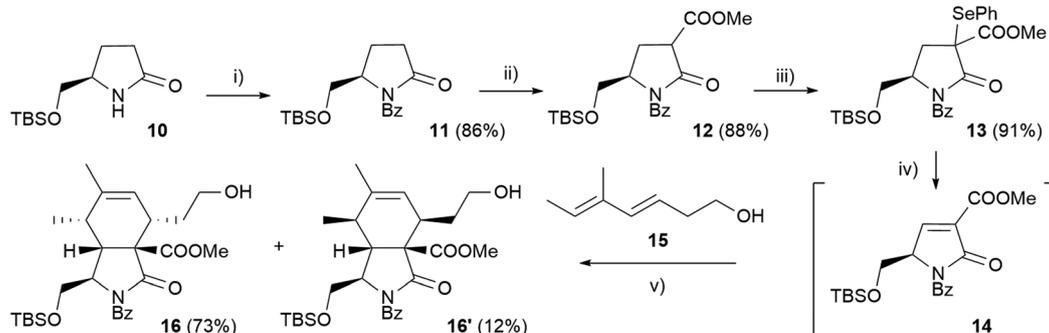
**Scheme 3** Reagents and conditions: (i) NaH, BzCl, THF, 0 °C to RT, 24 h; (ii) LiHMDS, ClCO₂Me, THF, -78 °C, 5.5 h; (iii) LiHMDS, PhSeCl, THF, -78 °C, 4 h; (iv) H₂O₂, DCM, RT, 2 h; (v) HFIP, 35 °C, 18 h.

Table 2). In this case, the reaction mixture contained fewer impurities, making the isolation of product **8** much easier.

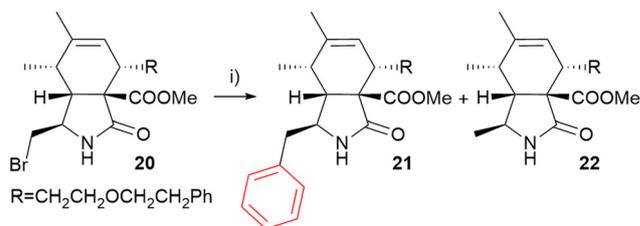
Following the initial screening of reaction conditions with pyrrolidone derivatives, we focused on the synthesis of the starting material **16** with a cytochalasan scaffold and a phenylalkyl side chain instead of the macrocycle (Scheme 3). This structural analogue was chosen based on our previous work showing that cytochalasan analogues lacking the macrocyclic moiety still exhibit biological activities.²¹ The key step of the synthesis is the formation of the perhydroisoindolone core by the Diels–Alder reaction. First, we considered *N*-MOM protection of a dienophile but the approach failed due to dienophile instability (data not shown). The presence of an electron-withdrawing protecting group, such as the benzoyl group, is required. The first step of the synthesis of dienophile **14** was a benzoylation of *O*-silylated pyrrolidone **10** using NaH and benzoyl chloride (Scheme 3) yielding *N*-benzoyl pyrrolidone **11** (86%).⁴⁸ An enolate was then generated *in situ* using lithium bis(trimethylsilyl)amide (LiHMDS) and reacted with methyl chloroformate to give acylated pyrrolidone **12** (88%).²⁷ Following a similar procedure, the phenylselenenyl group was introduced using LiHMDS and PhSeCl as an electrophile, yielding selenide **13** (91%).²¹ Both intermediates **12** and **13** were obtained as mixtures of diastereoisomers. While the diastereoisomers of acylated pyrrolidones **12** are inseparable, the selenides **13** can be separated by flash chromatography. However, separation was not necessary as the subsequent reactions led to the formation of the same dienophile. The oxidation and subsequent spontaneous elimination of selenide **13** with hydrogen peroxide produced the dienophile **14**, which had to be used immediately in the subsequent Diels–Alder reaction due to its limited stability. The Diels–Alder reaction was performed with either DCM or 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as a solvent. In both cases, a mixture of two diastereoisomers **16** (the intended *endo*-diastereoisomer) and **16'** (*exo*-diastereoisomer) was formed. The reaction in HFIP gave a higher yield (85% over two steps) and better diastereoselectivity (**16/16'** ratio: 5.8/1) compared to the reaction in DCM (56% over two steps, **16/16'** ratio: 4.5/1). Separation of the diastereoisomers was achieved by flash chromatography using an excess of silica.

The aliphatic side chain was introduced using our previously published procedure (Scheme 4).²¹ The hydroxy group of compound **16** was alkylated with a triflate that was generated *in situ* from (2-iodoethyl)benzene using silver triflate and

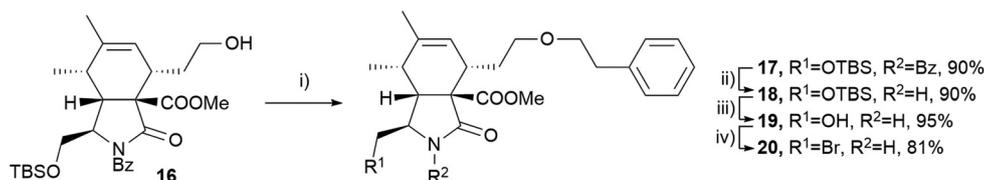
2,6-di-*tert*-butylpyridine. Derivative **17** was synthesized with a high yield of 90%. Subsequent steps involved the removal of the *O*- and *N*-protecting groups in derivative **17**. Optimal outcomes were achieved by employing Zemplén's conditions for the initial removal of the *N*-Bz protecting group. Following this step, the TBS group in the debenzoylated intermediate **18** was efficiently cleaved using (HF)₃·NEt₃, yielding the unprotected intermediate **19** (Scheme 4). It is noteworthy that the deprotection sequence can be reversed (*O*-deprotection followed by *N*-deprotection), however, in such case, a partial migration of the *N*-Bz group to the hydroxy group was observed (Scheme S2†). Finally, an Appel reaction of intermediate **19** with CBr₄ and PPh₃ smoothly led to the key bromide **20** (81%, Scheme 4).

Bromide **20** is more complex than pyrrolidone **7**, so conclusions drawn from arylations with a simple model compound may not be applicable. Therefore, both cobalt and iron catalysis were considered. We first investigated its reactivity in cobalt-mediated cross-coupling reactions with phenylmagnesium bromide (Scheme 5). However, the cobalt catalysts proved to be inefficient. Indeed, rapid screening of the reaction conditions (temperature, phenylmagnesium bromide equivalents, catalyst and ligand; entries 1–4, Table 3) resulted in poor conversion and the formation of the debrominated byproduct **22** at the expense of the target cross-coupling product **21**.

In contrast, our experiments with iron catalyst proved more promising. Building on the successful conditions for arylation of the model compound **7** with a substantial excess of Grignard reagent, subsequent attempts with the cytochalasan starting material **20** followed the same approach. Full conversion was achieved within 4.5 h (entry 5, Table 3). However, a mixture of products was formed: the desired phenylated compound **21** and a debrominated byproduct **22** (¹H NMR ratio of



Scheme 5 Optimization of the cross-coupling reaction using cytochalasan bromide **20**. Reagents and conditions: (i) PhMgBr, catalyst (0.05 eq.), ligand, THF (non-degassed), see Table 3.



Scheme 4 Reagents and conditions: (i) (2-iodoethyl)benzene, AgOTf, 2,6-di-*tert*-butylpyridine, DCM, RT to 35 °C, 72 h; (ii) Na, MeOH, RT, 2 h; (iii) (HF)₃·NEt₃, CH₃CN, RT, 5 h; (iv) CBr₄, PPh₃, DCM, RT, 2.5 h.



Table 3 Optimization of the cross-coupling reaction using cytochalasin bromide **20**. If not stated otherwise, non-degassed THF was used

Entry	PhMgBr (eq.)	Catalyst	Ligand (eq.)	Temperature	Time	NMR ratio 20 : 21 : 22
1	2.6	Co(acac) ₃	TMEDA (0.36)	55 °C	24 h	62 : 13 : 25
2	4.0	Co(acac) ₃	TMEDA (0.05)	RT	22 h	67 : 11 : 22
3	2.6	Co(PPh ₃) ₂ Cl ₂	TMEDA (0.05)	RT	22 h	88 : 4 : 8
4	2.6	Co(acac) ₃	XPhos (0.1)	RT	24 h	93 : 7 : 0
5	7.7	Fe(acac) ₃	TMEDA (0.05)	0 °C to RT	4.5 h	0 : 62 ^a : 38
6	7.7	Fe(acac) ₃	TMEDA (0.05)	0 °C to 50 °C	4.5 h	36 : 23 : 41
7	7.7	FeCl ₃	TMEDA (0.05)	0 °C to RT	4.5 h	38 : 35 : 27
8 ^b	7.7	Fe(acac) ₃	TMEDA (0.05)	0 °C to RT	4.5 h	42 : 24 : 34
9	7.7	Fe(acac) ₃	TMEDA (1.2)	0 °C to RT	4.5 h	43 : 26 : 31
10	7.7	Fe(acac) ₃	dppe (0.05)	0 °C to RT	4.5 h	49 : 20 : 31
11	7.7	Fe(acac) ₃	SIPr (0.05)	0 °C to RT	4.5 h	0 : 41 : 59
12	7.7	Fe(acac) ₃ ^c	TMEDA (1.00)	0 °C to RT	4.5 h	0 : 70 : 30

^a Isolated yield 36%. ^b Et₂O was used as a solvent. ^c 1.00 eq.

62/38; isolated yield of **21**: 36%; entry 5, Table 3). ¹H NMR yields were determined according to the chemical shifts of the signals that did not overlap (signal of H-13 of compound **20**: δ 3.35–3.25 ppm, compound **21**: δ 3.23 ppm, compound **22**: δ 3.15 ppm; see ESI†). It was crucial to achieve full conversion as the similar retention factors of bromide **20** and phenyl derivative **21** made their separation very difficult (compounds **20** and **21** are only separable by preparative HPLC) and precluded the possibility of monitoring the reaction by TLC. The reaction conditions were further optimized. However, changes in the reaction temperature, solvent, catalyst or amount and type of a ligand led to incomplete conversion and a decrease in the ratio of product **21** and byproduct **22** (entries 7–10, Table 3). Only the use of the SIPr ligand led to full conversion but the preferential formation of the debrominated byproduct **22** was observed (¹H NMR ratio of **21/22**: 41/59; entry 11, Table 3). Some alternative ligands were tested without improved results (for details, see ESI, Table S1†). Finally, stoichiometric amounts of both Fe(acac)₃ and TMEDA were used, leading to complete conversion and a **21/22** ratio of 70/30 (entry 12, Table 3). These conditions were found to be the most efficient for the arylation.

A series of cytochalasin analogues was synthesized by the arylation of bromide **20** with aryl Grignard reagents of various

sizes and substitutions (Scheme 6). Because the iron-mediated cross-coupling reactions with benzyl Grignard reagents have been reported,⁴⁹ a reaction with benzylmagnesium chloride was also included. Experiments conducted in both degassed and non-degassed THF yielded similar outcomes. The aromatic cytochalasin analogues **23–27** were isolated in modest yields (8–28%), along with the benzylic analogue **28** (7%). The reactions of bromide **20** with 2-pyridylmagnesium bromide or 1-naphthylmagnesium bromide did not yield the desired derivatives **29** and **30**, respectively. The low yields were attributed to incomplete conversion, formation of the debrominated byproduct **22**, and the challenging purification of the final products, requiring multiple rounds of flash chromatography and preparative HPLC. The inconvenience of incomplete conversion and difficult separation can be partially solved by treating the crude reaction product with sodium methoxide that substitutes the bromine of the unreacted starting material **20**. The substitution product can be easily removed from the mixture by chromatography. Despite the challenges of achieving optimal yields and purifications, our approach marks a significant milestone as the first successful introduction of a non-natural aryl moiety onto the cytochalasin scaffold.

Compounds **22–28** were screened for their cytotoxic activities against human melanoma BLM cell line and MRC-5 fibro-

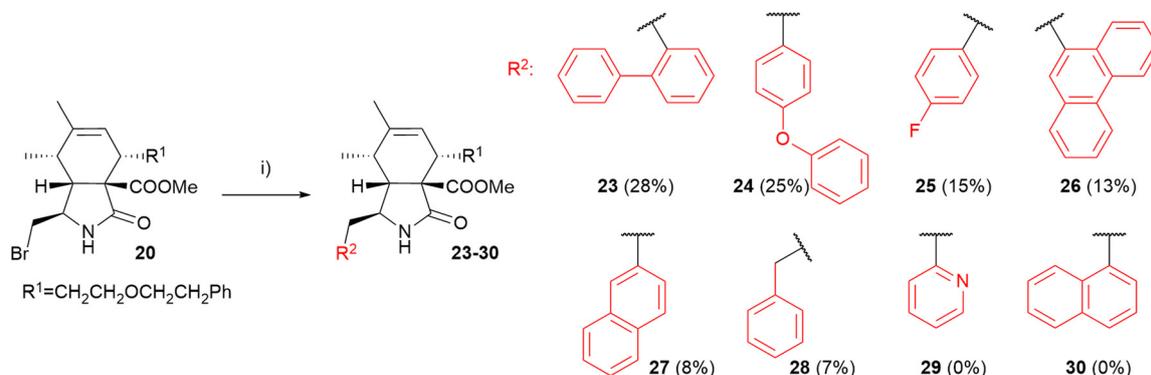
**Scheme 6** Reagents and conditions: (i) R²MgBr or R²MgCl (7.7 eq.), TMEDA (1 eq.), Fe(acac)₃ (1 eq.), THF, 0 °C to RT, 4.5–24 h.

Table 4 Cytotoxic activities of cytochalasan analogues **22–28** in human melanoma cells (BLM) and human fibroblasts (MRC-5) after 72 h treatment (measured by WST-1 assay). The IC₅₀ value represents half-maximal inhibitory concentration

Cell line Compound	BLM IC ₅₀ ± SEM [μM]	MRC-5
21 ^a	27.07 ± 1.24	30.50 ± 0.38
22	50	50
23	27.06 ± 1.61	30.76 ± 0.33
24	50	50
25	32.68 ± 3.09	39.30 ± 0.78
26	50	50
27	37.64 ± 3.39	42.13 ± 3.63
28	31.85 ± 4.30	39.41 ± 4.59

Values represent the mean that originates from at least three independent experiments and the standard error of the mean. ^a Values from ref. 21.

blasts (Table 4) after 72 h treatment. None of the compounds showed selectivity towards the cancer cell line. Compounds **23**, **25**, **27**, and **28** showed moderate activity similar to or lower than the cytotoxic effect of previously reported derivative **21**.²¹ On the other hand, after 72 h treatment, methyl derivative **22**, phenoxyphenyl **24** and phenanthrenyl **26** derivatives did not show sufficient activity (IC₅₀ > 50 μM), indicating that the presence of an aryl moiety improves the cytotoxic effect, however, the bulkiness, and/or sterical factors need to be considered to maintain the activity.

Experimentals

General remarks

Solvents and chemicals were either purchased from commercial suppliers or purified using standard techniques. *tert*-Butyldimethylsilylpyrrolidone **10**,³⁰ dienol **15** (ref. 50) and (2-iodoethyl)benzene⁵¹ were synthesized using previously published protocols. Flash chromatography was performed by using silica gel Silicycle – Siliaflash® P 60 (particle size 40–63 μm, pore diameter 60 Å). Thin-layer chromatography (TLC) was conducted using silica gel plates Merck 60 F254.

¹H, ¹³C, ¹⁹F NMR spectra were measured on Agilent 400-MR DDR2 or JEOL-ECZL400G (400.0 MHz for ¹H, 100.6 MHz for ¹³C, 376.0 MHz for ¹⁹F). The complete assignment of all NMR signals was done by a combination of H,H-COSY, H,H-ROESY, H,C-HSQC, and H,C-HMBC experiments. The spectra were recorded in CDCl₃. It served as an internal standard (δ_{CDCl₃} = 7.26 ppm) for ¹H NMR and (δ_{CDCl₃} = 77.0 ppm) for ¹³C NMR, CFCl₃ (δ_{CFCl₃} = 0.00 ppm) was used as an external standard for ¹⁹F NMR. Cytochalasan atom numbering was used for the assignment of the NMR signals.⁵² Low- and high-resolution mass spectroscopic data were obtained on LTQ Orbitrap XL (Thermo Fisher Scientific) using ESI at the Laboratory of Mass Spectrometry, IOCB Prague. Optical rotations were measured at 20 °C, and [α]_D values are given in 10⁻¹ deg cm² g⁻¹. Flash chromatography (FC) was performed using the Büchi Pure

C-815 Flash system on CHROMABOND Flash empty cartridges filled with silica gel Silicycle – Siliaflash® P 60 (particle size 40–63 μm, pore diameter 60 Å). Purification of some compounds was done by HPLC Büchi Pure C-850 FlashPrep system on a column packed with 5 μm normal phase (ProntoSIL 60-5-Si 150 × 20 mm, BISCHOFF Chromatography). The purity of all final compounds was determined by clean NMR spectra and by HPLC.

(R)-5-Benzyl-1-(methoxymethyl)pyrrolidin-2-one (6). Co(acac)₃ (2 mg, 5.63 μmol) was added to a dry Schlenk flask and evacuated and filled with argon (3×). A solution of **4** (25 mg, 0.11 mmol) in dry THF (0.5 mL), TMEDA (0.4 mL, 0.07 M in THF, 26.7 μmol) and THF (0.5 mL) were added and stirred for 5 minutes at RT under argon atmosphere. Then, phenylmagnesium bromide (91 μL, 1.6 M in cyclopentyl methyl ether (CPME), 0.15 mmol) was slowly added dropwise and the mixture was stirred at RT under argon atmosphere for 24 h. A solution of NH₄Cl (5 mL) and EtOAc (5 mL) were added and the resulting phases were separated. The aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (1 × 5 mL), dried (MgSO₄) and the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent: EtOAc in hexane 0% to 100%, the product elutes at 70%), affording the titled pyrrolidone **6** as a yellowish oil (22 mg, 88%). ¹H NMR (400 MHz, CDCl₃) δ 7.31 (m, ∑J = 18.0 Hz, 2H, H-*m*-Ph), 7.24 (m, ∑J = 17.6 Hz, 1H, H-*p*-Ph), 7.18 (m, ∑J = 12.3 Hz, 2H, H-*o*-Ph), 4.93 (d, J_{gem} = 10.5 Hz, 1H, NCH₂a), 4.62 (d, J_{gem} = 10.5 Hz, 1H, NCH₂b), 3.95 (ddt, J_{5,6b} = 9.0, J_{5,4a} = 7.7, J_{5,6a} = J_{5,4b} = 4.5 Hz, 1H, H-5), 3.31 (s, 3H, OCH₃), 3.16 (dd, J_{gem} = 13.3, J_{6a,5} = 4.4 Hz, 1H, H-6a), 2.60 (dd, J_{gem} = 13.4, J_{6b,5} = 9.0 Hz, 1H, H-6b), 2.28 (m, ∑J = 18.0 Hz, 2H, H-3a,b), 1.98 (ddt, J_{gem} = 12.9, J_{4a,3a} = 8.9, J_{4a,3b} = J_{4a,5} = 7.7 Hz, 1H, H-4a), 1.76 (dddd, J_{gem} = 13.1, J_{4b,3b} = 8.4, J_{4b,3a} = 7.2, J_{4b,5} = 4.8 Hz, 1H, H-4b) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 176.45 (C-2), 136.96 (C-*i*-Ph), 129.22 (C-*o*-Ph), 128.59 (C-*m*-Ph), 126.70 (C-*p*-Ph), 72.27 (NCH₂), 57.89 (CH₂-5), 56.04 (OCH₃), 39.62 (CH₂-6), 29.94 (CH₂-3), 23.82 (CH₂-4) ppm. HRMS (ESI) *m/z* calcd for C₁₃H₁₇O₂NNa [M + Na]⁺ 242.1152; found 242.1150.

(R)-5-Benzylpyrrolidin-2-one (8). Fe(acac)₃ (80 mg, 0.22 mmol) and (R)-5-(bromomethyl)pyrrolidin-2-one **7** (40 mg, 0.22 mmol) were added to a dry Schlenk flask and evacuated and filled with argon (3×). Then, TMEDA (34 μL, 0.22 mmol) and dry and degassed THF (0.5 mL) were added and the resulting mixture was cooled to 0 °C. Then, phenylmagnesium bromide (1.38 mL, 1.25 M in CPME, 1.73 mmol) was slowly added dropwise and the mixture was stirred at RT under argon atmosphere for 18 h. A solution of NH₄Cl (5 mL) and EtOAc (5 mL) were added, phases were separated and aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with a solution of NaHCO₃ and EDTA (4 × 5 mL), brine (1 × 5 mL), dried (MgSO₄) and the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent: EtOAc in hexane 0% to 100%, the product elutes at 100%), affording the titled pyrrolidone **8** as a yellowish oil (23 mg, 59%). ¹H NMR (400 MHz,



CDCl₃) δ 7.31 (ddd, $J_{H-m-Ph,H-o-Ph/H-p-Ph} = 7.4$, $J_{H-m-Ph,H-o-Ph/H-p-Ph} = 6.1$, $J_{H-m-Ph,H-m-Ph} = 1.3$ Hz, 2H, H-*m*-Ph), 7.24 (m, $\sum J = 17.5$ Hz, 1H, H-*p*-Ph), 7.17 (m, $\sum J = 12.3$ Hz, 2H, H-*o*-Ph), 6.11 (s, 1H, NH), 3.88 (m, $\sum J = 26.2$ Hz, 1H, H-5), 2.83 (dd, $J_{gem} = 13.4$, $J_{6a,5} = 5.7$ Hz, 1H, H-6a), 2.73 (dd, $J_{gem} = 13.4$, $J_{6b,5} = 7.9$ Hz, 1H, H-6b), 2.34–2.18 (m, 3H, 2 \times H-3, H-4a), 1.84 (m, $\sum J = 35.3$ Hz, 1H, H-4b) ppm, with agreement with the published data.³⁰

(R)-1-Benzoyl-5-[[*tert*-butyldimethylsilyloxy]methyl]pyrrolidin-2-one (11). This compound was synthesized in analogy with a known procedure.⁴⁸ To an ice-cooled solution of (R)-5-[[*tert*-butyldimethylsilyloxy]methyl]pyrrolidin-2-one **10** (14.2 g, 0.06 mol) in anhydrous THF (65 mL) was added NaH (60% oil dispersion, 3.0 g, 0.07 mol) under argon. After 30 minutes of stirring at 0 °C, benzoyl chloride (8.63 mL, 0.07 mol) was slowly added. It was further stirred for 10 h at 0 °C and 10 h at RT. The conversion was monitored by TLC (hexane/EtOAc: 7/2). Additional NaH (60% oil dispersion, 1.24 g, 0.03 mol) and benzoyl chloride (2.00 mL, 0.02 mol, 0.28 equiv.) were added at 0 °C. The reaction was stirred for 3 h, then quenched with crushed ice and water (50 mL) and allowed to warm to RT and extract with DCM (3 \times 150 mL). The combined organic layers were washed with brine (100 mL), dried (MgSO₄) and the solvents were evaporated *in vacuo*. The product was then purified twice by FC (eluent: EtOAc in hexane 0% to 100%), affording the titled pyrrolidone **11** as a white amorphous solid (17.8 g, 86%). ¹H NMR (400 MHz, CDCl₃) δ 7.58 (dd, $J_{o,m} = 8.1$ Hz, $J_{o,p} = 1.1$ Hz, 2H, H-*o*-Bz), 7.50 (tt, $J_{p,m} = 8.4$ Hz, $J_{p,o} = 1.3$ Hz, 1H, H-*p*-Bz), 7.40 (m, $\sum J = 14.9$ Hz, 2H, H-*m*-Bz), 4.57 (m, $\sum J = 17.2$ Hz, 1H, H-5), 4.11 (dd, $J_{gem} = 10.5$ Hz, $J_{OCH_2a,5} = 3.3$ Hz, 1H, OCH₂a), 3.73 (dd, $J_{gem} = 10.5$ Hz, $J_{OCH_2b,5} = 2.2$ Hz, 1H, OCH₂b), 2.81 (dt, $J_{gem} = 17.8$ Hz, $J_{3a,4a} = J_{3a,4b} = 9.7$ Hz, 1H, H-3a), 2.47 (ddd, $J_{gem} = 17.8$ Hz, $J_{3b,4a} = 9.8$ Hz, $J_{3b,4b} = 3.9$ Hz, 1H, H-3b), 2.33–2.10 (m, 2H, H-4a,b), 0.89 (s, 9H, C(CH₃)₃), 0.06 (s, 3H, SiCH₃), 0.02 (s, 3H, SiCH₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 175.55 (C-2), 170.88 (C=O-Bz), 134.98 (C-*i*-Bz), 131.80 (CH-*p*-Bz), 128.71 (CH-*o*-Bz), 127.85 (CH-*m*-Bz), 63.70 (CH₂-OSi), 58.63 (CH-5), 32.71 (CH₂-3), 25.87 (SiCCH₃), 21.25 (CH₂-4), 18.21 (SiCCH₃), -5.47 (SiCH₃), -5.60 (SiCH₃) ppm. HRMS (ESI) *m/z* calcd for C₁₈H₂₈O₃NSi [M + H]⁺ 334.1833; found 334.1835.

Methyl (5R)-1-benzoyl-5-[[*tert*-butyldimethylsilyloxy]methyl]-2-oxopyrrolidine-3-carboxylate (12). This compound was synthesized in analogy with a known procedure.²⁷ To a solution of compound **11** (100 mg, 0.30 mmol) in anhydrous THF (1 mL), LiHMDS (0.60 mL, 1.0 M in THF, 0.60 mmol) was added at -78 °C under argon. The reaction mixture was allowed to stir at -78 °C for 30 minutes before methyl chloroformate (47.0 μ L, 0.60 mmol) was added. The conversion was monitored by TLC (hexane/EtOAc: 4/1). After 5 h, the resulting mixture was quenched with saturated aq. NaHCO₃ (15 mL) and extracted with EtOAc (3 \times 15 mL). The combined organic layers were washed with brine (15 mL), dried (MgSO₄) and the solvents were evaporated *in vacuo*. The product was purified by FC (eluent: EtOAc in hexane 0% to 20%) to give **12** (103 mg, 88%) as a 4/1 diastereomeric mixture, a yellow dense oil. ¹H

NMR (400 MHz, CDCl₃) δ 7.68 (dd, $J_{o,m} = 8.4$ Hz, $J_{o,p} = 1.3$ Hz, 2H, H-*o*-Bz min.), 7.56 (dd, $J_{o,m} = 8.4$ Hz, $J_{o,m} = 1.4$ Hz, 2H, H-*o*-Bz maj.), 7.53–7.47 (m, 2H, H-*p*-Bz min. + H-*p*-Bz maj.), 7.43–7.36 (m, 4H, H-*m*-Bz min. + H-*m*-Bz maj.), 4.64 (m, $\sum J = 15.7$ Hz, 1H, H-5 maj.), 4.46 (m, $\sum J = 22.8$ Hz, 1H, H-5 min.), 4.16 (dd, $J_{gem} = 10.7$, $J_{OCH_2a,5} = 2.7$ Hz, 1H, OCH₂a maj.), 4.02 (dd, $J_{gem} = 10.4$, $J_{OCH_2a,5} = 4.7$ Hz, 1H, OCH₂a min.), 3.93 (m, $\sum J = 19.6$ Hz, 1H, H-3 maj.), 3.80 (s, 3H, OCH₃ min.), 3.76 (s, 3H, OCH₃ maj.), 3.76–3.69 (m, 2H, OCH₂b maj. + OCH₂b min.), 3.58 (dd, $J_{3,4a} = 10.1$, $J_{3,4b} = 9.0$ Hz, 1H, H-3 min.), 2.73–2.59 (m, 2H, H-4a maj. + H-4a min.), 2.42 (m, $\sum J = 31.6$ Hz, 1H, H-4b min.), 2.34 (m, $\sum J = 24.2$ Hz, 1H, H-4b maj.), 0.89 (s, 9H, C(CH₃)₃ maj.), 0.87 (s, 9H, C(CH₃)₃ min.), 0.06 (s, 3H, SiCH₃ maj.), 0.034 (s, 3H, SiCH₃ min.), 0.029 (s, 3H, SiCH₃ maj.), -0.04 (s, 3H, SiCH₃ min.) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 171.02 (C=O-Bz min.), 170.51 (C=O-Bz/C-2 maj.), 170.39 (C=O-Bz/C-2 maj.), 170.34 (C-2 min.), 169.84 (COOCH₃ maj.), 169.31 (COOCH₃ min.), 134.30 (C-*i*-Bz maj.), 133.97 (C-*i*-Bz min.), 132.67 (CH-*p*-Bz, min.), 131.97 (CH-*p*-Bz, maj.), 129.52 (CH-*o*-Bz min.), 128.61 (CH-*o*-Bz maj.), 127.98 (CH-*m*-Bz min.), 127.92 (CH-*m*-Bz maj.), 64.07 (CH₂-OSi maj.), 61.29 (CH₂-OSi min.), 57.08 (CH-5 maj.), 57.00 (CH-5 min.), 52.90 (COOCH₃ min.), 52.85 (COOCH₃ maj.), 50.09 (CH-3 maj.), 49.04 (CH-3 min.), 26.04 (CH₂-4 maj.), 25.86 (SiCCH₃ maj.), 25.77 (SiCCH₃ min.), 23.93 (CH₂-4 min.), 18.22 (SiCCH₃ min.), 18.19 (SiCCH₃ maj.), -5.50 (SiCH₃ maj.), -5.54 (SiCH₃ min.), -5.61 (SiCH₃ min.), -5.63 (SiCH₃ maj.) ppm. HRMS (ESI) *m/z* calcd for C₂₀H₃₀O₅NSi [M + H]⁺ 392.1888; found 392.1885.

Methyl (5R)-1-benzoyl-5-[[*tert*-butyldimethylsilyloxy]methyl]-2-oxo-3-(phenylselanyl)pyrrolidine-3-carboxylate (13). This compound was synthesized in analogy with a known procedure.²¹ To a solution of compound **12** (100 mg, 0.26 mmol) in anhydrous THF (1 mL), LiHMDS (0.38 mL, 1.0 M in THF, 0.38 mmol) was added at -78 °C under argon. After 1 h, a solution of PhSeCl (74 mg, 0.38 mmol) in dry THF (1 mL) was added dropwise and the reaction mixture was stirred at -78 °C until full conversion (3 h, TLC, hexanes/EtOAc: 4/1). The resulting mixture was quenched with saturated aq. NH₄Cl (1 mL), warmed to RT, poured into a solution of NH₄Cl (10 mL) and extracted with EtOAc (3 \times 15 mL). The combined organic layers were washed with brine (15 mL), dried (MgSO₄) and the solvents were evaporated *in vacuo*. The diastereomeric mixture was purified by FC on silica (eluent: EtOAc in hexane 0% to 18%), affording the two diastereomers **13** (major: 89 mg, 64%; minor: 39 mg, 27%) as yellow dense oils. **Major:** ¹H NMR (400 MHz, CDCl₃) δ 7.67–7.63 (m, 4H, H-*o*-PhSe, H-*o*-Bz), 7.52 (m, $\sum J = 17.2$ Hz, 1H, H-*p*-Bz), 7.46–7.37 (m, 3H, 2 \times H-*m*-Bz, H-*p*-PhSe), 7.32 (m, $\sum J = 19.1$ Hz, 2H, H-*m*-PhSe), 4.08 (dddd, $J_{5,4b} = 7.9$, $J_{5,4a} = 7.0$, $J_{5,OCH_2a} = 3.9$, $J_{5,OCH_2b} = 2.2$ Hz, 1H, H-5), 3.96 (dd, $J_{gem} = 10.7$, $J_{OCH_2a,5} = 3.9$ Hz, 1H, OCH₂a), 3.76 (s, 3H, OCH₃), 3.55 (dd, $J_{gem} = 10.7$, $J_{OCH_2b,5} = 2.2$ Hz, 1H, OCH₂b), 2.99 (dd, $J_{gem} = 14.4$, $J_{4a,5} = 7.0$ Hz, 1H, H-4a), 2.34 (dd, $J_{gem} = 14.4$, $J_{4b,5} = 8.0$ Hz, 1H, H-4b), 0.83 (s, 9H, C(CH₃)₃), -0.03 (s, 3H, SiCH₃), -0.09 (s, 3H, SiCH₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 170.75 (C=O-Bz), 170.07 (C-2), 169.32 (COOCH₃),



137.76 (CH-*o*-PhSe), 134.04 (C-*i*-Bz), 132.37 (CH-*p*-Bz), 130.22 (CH-*p*-PhSe), 129.29 (CH-*o*-Bz/CH-*m*-PhSe), 129.19 (CH-*o*-Bz/CH-*m*-PhSe), 127.85 (CH-*m*-Bz), 126.05 (C-*i*-PhSe), 61.05 (CH₂-OSi), 55.64 (CH-5), 53.96 (COOCH₃), 53.38 (C-3), 31.92 (CH₂-4), 25.72 (SiCCH₃), 18.20 (SiCCH₃), -5.62 (SiCH₃), -5.70 (SiCH₃) ppm. HRMS (ESI) *m/z* calcd for C₂₆H₃₄O₅N⁸⁰SeSi [M + H]⁺ 548.1366; found 548.1363. **Minor:** ¹H NMR (400 MHz, CDCl₃) δ 7.73 (dd, *J*_{H-*o*-PhSe,H-*m*-PhSe} = 8.2, *J*_{H-*o*-PhSe,H-*p*-PhSe} = 1.3 Hz, 2H, H-*o*-PhSe), 7.59 (m, ∑*J* = 8.4 Hz, 2H, H-*o*-Bz), 7.54 (m, ∑*J* = 17.5 Hz, 1H, H-*p*-Bz), 7.47–7.32 (m, 5H, 2× H-*m*-Bz, 2× H-*m*-PhSe, H-*p*-PhSe), 4.42 (tdd, *J*_{5,4a,b} = 7.6, *J*_{5,OCH₃a} = 5.0, *J*_{5,OCH₃b} = 2.6 Hz, 1H, H-5), 3.95 (dd, *J*_{gem} = 10.4, *J*_{OCH₃a,5} = 5.0 Hz, 1H, OCH₂a), 3.72–3.64 (m, 4H, OCH₃ + OCH₂b), 2.78 (dd, *J*_{gem} = 13.9, *J*_{4a,5} = 7.4 Hz, 1H, H-4a), 2.53 (dd, *J*_{gem} = 14.0, *J*_{4b,5} = 7.9 Hz, 1H, H-4b), 0.85 (s, 9H, C(CH₃)₃), -0.02 (s, 3H, SiCH₃), -0.08 (s, 3H, SiCH₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 171.07 (C=O-Bz), 170.04 (C-2), 169.35 (COOCH₃), 137.95 (CH-*o*-PhSe), 133.84 (C-*i*-Bz), 132.67 (CH-*p*-Bz), 129.98 (CH-*p*-PhSe), 129.57 (CH-*o*-Bz), 129.12 (CH-*m*-PhSe), 127.88 (CH-*m*-Bz), 126.27 (C-*i*-PhSe), 60.72 (CH₂-OSi), 56.51 (CH-5), 54.36 (C-3), 53.53 (COOCH₃), 32.24 (CH₂-4), 25.87 (SiCCH₃), 18.25 (SiCCH₃), -5.46 (SiCH₃), -5.60 (SiCH₃) ppm. HRMS (ESI) *m/z* calcd for C₂₆H₃₄O₅N⁸⁰SeSi [M + H]⁺ 548.1366; found 548.1363.

Methyl (1R,3aR,4S,7S,7aR)-2-benzoyl-1-[[tert-butyl(dimethylsilyl)oxy]methyl]-4-(2-hydroxyethyl)-6,7-dimethyl-3-oxo-1,2,3,4,7,7a-hexahydro-3aH-isoindole-3a-carboxylate (16) and methyl (1R,3aR,4R,7R,7aR)-2-benzoyl-1-[[tert-butyl(dimethylsilyl)oxy]methyl]-4-(2-hydroxyethyl)-6,7-dimethyl-3-oxo-1,2,3,4,7,7a-hexahydro-3aH-isoindole-3a-carboxylate (16'). An aqueous hydrogen peroxide (30%, 246 μL, 2.41 mmol) was added dropwise to a stirred solution of **13** (329 mg, 0.60 mmol) in DCM (5 mL) at 0 °C. Then, the reaction mixture was vigorously stirred at 0 °C for 15 min and subsequently at RT until full conversion was observed (2 h, TLC, hexanes/EtOAc: 4/1). A solution of NaHCO₃ (5 mL) was added and the resulting mixture was extracted with DCM (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried (MgSO₄) and the solvent was evaporated *in vacuo*. Diene **15** (76 mg, 0.60 mmol) and HFIP (1 mL) were added and the mixture was stirred at 35 °C for 18 h. The diastereomeric mixture was purified by FC on silica (eluent: EtOAc in hexane 0% to 30%), affording two diastereomers **16** (225 mg, 73%) and **16'** (39 mg, 12%) both as yellow dense oils. **16:** ¹H NMR (400 MHz, CDCl₃) δ 7.67 (dd, *J*_{o,m} = 8.4, *J*_{o,p} = 1.4 Hz, 2H, H-*o*-Bz), 7.52 (tt, *J*_{p,m} = 8.4 Hz, *J*_{p,o} = 1.5 Hz, 1H, H-*p*-Bz), 7.40 (m, ∑*J* = 14.8 Hz, 2H, H-*m*-Bz), 5.48 (m, ∑*J* = 10.9 Hz, 1H, H-7), 4.03 (td, *J*_{3,10} = 4.5, *J*_{3,4} = 2.9 Hz, 1H, H-3), 3.88 (dd, *J*_{gem} = 10.4, *J*_{10a,3} = 4.6 Hz, 1H, H-10a), 3.84 (s, 3H, OCH₃), 3.73–3.54 (m, 3H, H-14,10b), 2.88 (dd, *J*_{4,3} = *J*_{4,5} = 4.7 Hz, 1H, H-4), 2.83 (m, ∑*J* = 25.0 Hz, 1H, H-8), 2.63 (m, ∑*J* = 36.0 Hz, 1H, H-5), 2.02 (m, ∑*J* = 36.6 Hz, 1H, H-13a), 1.87 (m, ∑*J* = 32.7 Hz, 1H, H-13b), 1.79 (s, 3H, H-12), 1.26 (d, *J*_{11,5} = 7.3 Hz, 3H, H-11), 0.87 (s, 9H, C(CH₃)₃), 0.00 (s, 3H, SiCH₃), -0.02 (s, 3H, SiCH₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 172.74 (C-1/COOCH₃), 172.63 (C-1/COOCH₃), 170.61 (C=O-Bz), 140.81 (C-6), 134.31 (C-*i*-Bz), 132.32 (C-*p*-Bz), 129.07 (C-*o*-Bz), 127.92 (C-*m*-Bz), 126.36 (C-7), 62.68 (C-9), 62.14 (C-10), 61.48 (C-14),

58.03 (C-3), 53.00 (COOCH₃), 46.25 (C-4), 37.69 (C-8), 34.39 (C-5), 33.16 (C-13), 25.83 (SiCCH₃), 20.08 (C-12), 18.34 (SiCCH₃), 13.78 (C-11), -5.54 (SiCH₃), -5.63 (SiCH₃) ppm. HRMS (ESI) *m/z* calcd for C₂₈H₄₁O₆NNaSi [M + Na]⁺ 538.2595; found 538.2598. **16':** ¹H NMR (400 MHz, CDCl₃) δ 7.72 (m, ∑*J* = 8.0 Hz, 2H, H-*o*-Bz), 7.53 (m, ∑*J* = 20.0 Hz, 1H, H-*p*-Bz), 7.41 (ddd, *J*_{m,p} = *J*_{m,o} = 7.6, *J*_{m,m} = 1.8 Hz, 2H, H-*m*-Bz), 5.48 (m, ∑*J* = 10.0 Hz, 1H, H-7), 4.21 (ddd, *J*_{3,4} = 6.0, *J*_{3,10a} = 5.0, *J*_{3,10b} = 3.0 Hz, 1H, H-3), 3.92 (dd, *J*_{gem} = 10.5, *J*_{10a,3} = 5.0 Hz, 1H, H-10a), 3.78–3.67 (m, 5H, OCH₃, H-10b,14a), 3.58 (ddd, *J*_{gem} = 11.0, *J*_{14b,13a} = 8.5, *J*_{14b,13b} = 5.3 Hz, 1H, H-14b), 2.71 (dd, *J*_{4,3} = *J*_{4,5} = 5.9 Hz, 1H, H-4), 2.47 (m, ∑*J* = 20.0 Hz, 1H, H-8), 2.15–2.01 (m, 2H, H-5,13a), 1.84–1.66 (m, 4H, H-12,13b), 1.18 (d, *J*_{11,5} = 7.1 Hz, 3H, H-11), 0.87 (s, 9H, C(CH₃)₃), 0.02 (s, 3H, SiCH₃), -0.04 (s, 3H, SiCH₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 173.63 (C-1), 171.28 (COOCH₃), 171.02 (C=O-Bz), 136.91 (C-6), 134.09 (C-*i*-Bz), 132.59 (C-*p*-Bz), 129.45 (C-*o*-Bz), 127.93 (C-*m*-Bz), 124.17 (C-7), 61.11 (C-3), 60.95 (C-14), 60.25 (C-10), 58.69 (C-9), 52.36 (COOCH₃), 45.57 (C-4), 34.56 (C-5), 34.19 (C-8), 34.06 (C-13), 25.73 (SiCCH₃), 21.10 (C-12), 18.20 (SiCCH₃), 17.93 (C-11), -5.58 (SiCH₃), -5.66 (SiCH₃) ppm. HRMS (ESI) *m/z* calcd for C₂₈H₄₁O₆NNaSi [M + Na]⁺ 538.2595; found 538.2591.

Methyl (1R,3aR,4S,7S,7aR)-2-benzoyl-1-[[tert-butyl(dimethylsilyl)oxy]methyl]-6,7-dimethyl-3-oxo-4-(2-phenethoxyethyl)-1,2,3,4,7,7a-hexahydro-3aH-isoindole-3a-carboxylate (17). This compound was synthesized in analogy with a known procedure.²¹ AgOTf (2.4 g, 9.3 mmol) was dried under a high vacuum (heat gun 150–200 °C). Then, a solution of compound **16** (1.6 g, 3.1 mmol) in dry DCM (3 mL) followed by 2,6-di-*tert*-butylpyridine (2.4 mL, 10.9 mmol) and dry DCM (20 mL) were added at 0 °C under argon atmosphere. Subsequently, the (2-iodoethyl)benzene (1.4 mL, 9.9 mmol) was added and the resulting yellow suspension was stirred for 57 h at room temperature and for 14 h at 32 °C. The reaction mixture was filtered through a small pad of Celite and the organic layer was washed with 1 M HCl (15 mL), a solution of NaHCO₃ (15 mL) and brine (15 mL) and was dried (MgSO₄). The solvent was evaporated *in vacuo*. FC of the residue on silica (eluent: EtOAc in hexane 0% to 30%) furnished compound **17** (1.7 g, 90%) as a yellowish dense oil. ¹H NMR (400 MHz, CDCl₃) δ 7.67 (dd, *J*_{o,m} = 7.7, *J*_{o,p} = 1.3 Hz, 2H, H-*o*-Bz), 7.50 (t, *J*_{p,m} = 7.4 Hz, 1H, H-*p*-Bz), 7.40 (dd, *J*_{m,p} = *J*_{m,o} = 7.8 Hz, 2H, H-*m*-Bz), 7.28–7.16 (m, 5H, H-*o*,*m*,*p*-Ph), 5.48 (m, ∑*J* = 16 Hz, 1H, H-7), 4.04 (m, ∑*J* = 11.5 Hz, 1H, H-3), 3.86 (dd, *J*_{gem} = 10.4, *J*_{10a,3} = 4.8 Hz, 1H, H-10a), 3.81 (s, 3H, OCH₃), 3.67–3.39 (m, 5H, H-10b,14,15), 2.89 (dd, *J*_{4,3} = *J*_{4,5} = 4.6 Hz, 1H, H-4), 2.83 (t, *J*_{16,15} = 7.1 Hz, 2H, H-16), 2.73 (m, ∑*J* = 9.2 Hz, 1H, H-8), 2.59 (m, ∑*J* = 24.5 Hz, 1H, H-5), 2.05 (m, ∑*J* = 39.2 Hz, 1H, H-13a), 1.86 (m, ∑*J* = 28.0 Hz, 1H, H-13b), 1.78 (s, 3H, H-12), 1.26 (d, *J*_{11,5} = 7.3 Hz, 3H, H-11), 0.87 (s, 9H, C(CH₃)₃), 0.01 (s, 3H, SiCH₃), -0.01 (s, 3H, SiCH₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 172.59 (C-1/COOCH₃), 172.47 (C-1/COOCH₃), 170.62 (C=O-Bz), 140.35 (C-6), 139.20 (C-*i*-Ph), 134.41 (C-*i*-Bz), 132.20 (C-*p*-Bz), 129.03 (C-*o*-Bz), 128.91 (C-*o*-Ph), 128.18 (C-*m*-Ph), 127.89 (C-*m*-Bz), 126.41 (C-7), 125.98 (C-*p*-Ph), 71.34 (C-15), 69.40 (C-14), 62.79 (C-10), 62.54 (C-9), 57.69 (C-3), 52.80 (COOCH₃), 46.06 (C-4),



38.32 (C-8), 36.28 (C-16), 34.36 (C-5), 29.55 (C-13), 25.83 (SiCCH₃), 20.03 (C-12), 18.34 (SiCCH₃), 13.63 (C-11), -5.55 (SiCH₃), -5.62 (SiCH₃) ppm. HRMS (ESI) *m/z* calcd for C₃₆H₄₉O₆NNaSi [M + Na]⁺ 642.3221; found 642.3223.

Methyl (1R,3aR,4S,7S,7aR)-1-[[tert-butyl(dimethylsilyloxy)methyl]-6,7-dimethyl-3-oxo-4-(2-phenethoxyethyl)-1,2,3,4,7,7a-hexahydro-3aH-isoindole-3a-carboxylate (18). To a solution of **17** (143 mg, 0.23 mmol) in dry MeOH (5 mL), a small piece of sodium (approx. 3 × 3 × 3 mm) was added and the resulting mixture was stirred for 2 h at RT under argon atmosphere. A solution of NH₄Cl (0.5 mL) was slowly added and the resulting mixture was concentrated under reduced pressure. The residue was taken up in H₂O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried (MgSO₄) and the solvent was evaporated *in vacuo*. Purification *via* FC on silica gel (eluent: EtOAc in hexane 0% to 60%, the product elutes at 45% EtOAc) gave the title compound **18** as a yellowish dense oil (107 mg, 90%). ¹H NMR (400 MHz, CDCl₃) δ 7.29–7.15 (m, 5H, H-*o,m,p*-Ph), 5.90 (s, 1H, NH), 5.52 (m, ∑*J* = 11.5 Hz, 1H, H-7), 3.75 (s, 3H, OCH₃), 3.68 (dt, *J*_{gem} = 9.4, *J*_{15a,16a} = *J*_{15a,16b} = 7.2 Hz, 1H, H-15a), 3.62–3.49 (m, 4H, H-10a,14,15b), 3.40 (t, *J*_{gem} = *J*_{10b,3} = 9.6 Hz, 1H, H-10b), 3.10 (dt, *J*_{3,4} = 9.2, *J*_{3,10a} = *J*_{3,10b} = 4.7 Hz, 1H, H-3), 2.87 (t, *J*_{16,15a} = *J*_{16,15b} = 7.2 Hz, 2H, H-16), 2.72 (m, ∑*J* = 11.1 Hz, 1H, H-8), 2.44 (m, ∑*J* = 24.1 Hz, 1H, H-5), 2.28 (t, *J*_{4,5} = *J*_{4,3} = 4.5 Hz, 1H, H-4), 2.14 (m, ∑*J* = 31.4 Hz, 1H, H-13a), 1.91 (ddt, *J*_{gem} = 14.0, *J*_{13b,8} = 11.1, *J*_{13b,14} = 5.5 Hz, 1H, H-13b), 1.75 (s, 3H, H-12), 1.13 (d, *J*_{11,5} = 7.3 Hz, 3H, H-11), 0.89 (s, 9H, C(CH₃)₃), 0.06 (s, 6H, 2 × SiCH₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 173.57 (C-1), 173.08 (COOCH₃), 139.28 (C-*i*-Ph), 138.98 (C-6), 128.96 (C-*o*-Ph), 128.18 (C-*m*-Ph), 126.78 (C-7), 125.96 (C-*p*-Ph), 71.32 (C-15), 69.84 (C-14), 67.95 (C-10), 59.83 (C-9), 55.88 (C-3), 52.65 (COOCH₃), 50.31 (C-4), 36.43 (C-8), 36.34 (C-16), 33.80 (C-5), 29.97 (C-13), 25.82 (SiCCH₃), 20.21 (C-12), 18.23 (SiCCH₃), 14.04 (C-11), -5.42 (SiCH₃) ppm. HRMS (ESI) *m/z* calcd for C₂₉H₄₅O₅NNaSi [M + Na]⁺ 538.2959; found 538.2956.

Methyl (1R,3aR,4S,7S,7aR)-1-(hydroxymethyl)-6,7-dimethyl-3-oxo-4-(2-phenethoxyethyl)-1,2,3,4,7,7a-hexahydro-3aH-isoindole-3a-carboxylate (19). Triethylamine trihydrofluoride (203 μL, 1.24 mmol) was added to a solution of compound **18** (107 mg, 0.21 mmol) in dry acetonitrile (3 mL) at RT under argon atmosphere and the resulting mixture was stirred until full conversion (5 h, TLC, EtOAc). A solution of NaHCO₃ (5 mL) was slowly added (release of gas) and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried (MgSO₄) and the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc in hexane 50% to 100%, the product elutes at 100%) to give **19** (79 mg, 95%) as a yellowish dense oil. ¹H NMR (400 MHz, CDCl₃) δ 7.45 (s, 1H, NH), 7.30–7.15 (m, 5H, H-*o,m,p*-Ph), 5.49 (m, ∑*J* = 13.2 Hz, 1H, H-7), 3.74 (s, 3H, OCH₃), 3.69–3.47 (m, 5H, H-10a,14,15), 3.38 (m, ∑*J* = 18.9 Hz, 1H, H-10b), 3.19 (m, ∑*J* = 15.4 Hz, 1H, H-3), 2.86 (t, *J*_{16,15a} = *J*_{16,15b} = 7.2 Hz, 2H, H-16), 2.71 (m, ∑*J* = 17.7 Hz, 1H, H-8), 2.50–2.37

(m, 2H, H-4,5), 2.01 (m, ∑*J* = 31.1 Hz, 1H, H-13a), 1.90 (m, ∑*J* = 37.6 Hz, 1H, H-13b), 1.74 (s, 3H, H-12), 1.14 (d, *J*_{11,5} = 7.2 Hz, 3H, H-11) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 175.29 (C-1), 173.28 (COOCH₃), 139.42 (C-6), 139.19 (C-*i*-Ph), 128.91 (C-*o*-Ph), 128.19 (C-*m*-Ph), 126.33 (C-7), 125.98 (C-*p*-Ph), 71.39 (C-15), 69.69 (C-14), 66.52 (C-10), 60.63 (C-9), 56.60 (C-3), 52.66 (COOCH₃), 49.87 (C-4), 36.50 (C-8), 36.29 (C-16), 33.92 (C-5), 30.04 (C-13), 20.17 (C-12), 13.84 (C-11) ppm. HRMS (ESI) *m/z* calcd for C₂₃H₃₀O₅N [M – H][–] 400.2130; found 400.2128.

Methyl (1R,3aR,4S,7S,7aR)-1-(bromomethyl)-6,7-dimethyl-3-oxo-4-(2-phenethoxyethyl)-1,2,3,4,7,7a-hexahydro-3aH-isoindole-3a-carboxylate (20). To a solution of compound **19** (36 mg, 89.7 μmol) in dry DCM (3 mL), Ph₃P (54 mg, 0.21 mmol) and CBr₄ (68 mg, 0.21 mmol) were added at RT under argon atmosphere and the resulting mixture was stirred until full conversion (2.5 h, TLC, EtOAc). Then, the mixture was concentrated under reduced pressure and the crude product was purified by flash chromatography on silica gel (eluent: EtOAc in hexane 0% to 100%, the product elutes at 66%) to give **20** (34 mg, 81%) as a colorless dense oil. ¹H NMR (400 MHz, CDCl₃) δ 7.29–7.16 (m, 5H, H-*o,m,p*-Ph), 6.02 (s, 1H, NH), 5.53 (m, ∑*J* = 11.3 Hz, 1H, H-7), 3.77 (s, 3H, OCH₃), 3.67 (dt, *J*_{gem} = 9.3, *J*_{15a,16a} = *J*_{15a,16b} = 7.1 Hz, 1H, H-15a), 3.61–3.50 (m, 3H, H-14,15b), 3.41 (m, ∑*J* = 7.0 Hz, 1H, H-10a), 3.35–3.25 (m, 2H, H-3,10b), 2.87 (t, *J*_{16,15a} = *J*_{16,15b} = 7.1 Hz, 2H, H-16), 2.70 (m, ∑*J* = 13.3 Hz, 1H, H-8), 2.52–2.42 (m, 2H, H-4,5), 2.13 (m, ∑*J* = 31.7 Hz, 1H, H-13a), 1.91 (m, ∑*J* = 38.8 Hz, 1H, H-13b), 1.76 (s, 3H, H-12), 1.18 (d, *J*_{11,5} = 7.0 Hz, 3H, H-11) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 173.30 (C-1), 172.58 (COOCH₃), 139.22 (C-*i*-Ph), 138.61 (C-6), 128.92 (C-*o*-Ph), 128.16 (C-*m*-Ph), 126.96 (C-7), 125.95 (C-*p*-Ph), 71.31 (C-15), 69.66 (C-14), 60.42 (C-9), 55.52 (C-3), 53.46 (C-4), 52.78 (COOCH₃), 37.66 (C-10), 36.55 (C-8), 36.29 (C-16), 33.85 (C-5), 29.83 (C-13), 20.10 (C-12), 14.02 (C-11) ppm. HRMS (ESI) *m/z* calcd for C₂₃H₃₀O₄N⁷⁹BrNa [M + Na]⁺ 486.1250; found 486.1245.

General procedure for cross-coupling reactions

Fe(acac)₃ (1.00 eq.) was added to a dry Schlenk flask that was then evacuated and filled with argon (3×). A solution of compound **19** (1.00 eq.) in anhydrous THF (0.5–1 mL), TMEDA (1.00 eq.) and THF (0.5–1 mL) were added and the resulting mixture was cooled to 0 °C. Then, a Grignard reagent (7.7 eq.) was slowly added dropwise and the mixture was stirred at RT under argon atmosphere for 4.5–24 h. A solution of NH₄Cl (5 mL) and EtOAc (5 mL) were added, phases were separated and aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with a solution of NaHCO₃ and EDTA (4 × 5 mL) and brine (1 × 5 mL) and was dried (MgSO₄) and the solvent was evaporated *in vacuo*. The crude products were purified by flash chromatography and preparative HPLC on silica gel (eluent: EtOAc in hexane 0% to 80%). The debrominated compound **22** was formed as a byproduct.

Methyl (1S,3aR,4S,7S,7aR)-1-benzyl-6,7-dimethyl-3-oxo-4-(2-phenethoxyethyl)-1,2,3,4,7,7a-hexahydro-3aH-isoindole-3a-carboxylate (21). By following the slightly modified general pro-



cedure (a different number of equivalents was used), the cross-coupling reaction was carried out with a solution of Fe(acac)₃ (13 μL, 0.1 M in THF, 1.19 μmol), **19** (11 mg, 23.7 μmol) in dry THF (0.5 mL), a solution of TMEDA (18 μL, 0.07 M in THF, 1.19 μmol), PhMgBr (114 μL, 1.6 M in CPME, 0.18 mmol) and dry THF (0.3 mL). FC (eluent: EtOAc in hexane 0% to 80%, the product elutes at 50% EtOAc) furnished compound **21** (4 mg, 36%) as a yellowish dense oil. ¹H NMR (400 MHz, CDCl₃) δ 7.35–7.14 (m, 10H, Ph, Bn), 5.50 (m, 2H, NH, H-7), 3.78 (s, 3H, OCH₃), 3.71–3.48 (m, 4H, H-14,15), 3.23 (ddd, *J*_{3,10a} = 9.0, *J*_{3,4} = *J*_{3,10b} = 4.4 Hz, 1H, H-3), 2.88 (m, 3H, H-10b,16), 2.71 (m, $\sum J$ = 16.1 Hz, 1H, H-8), 2.67–2.55 (m, 2H, H-4,10a), 2.48 (m, $\sum J$ = 36.9 Hz, 1H, H-5), 2.11 (m, $\sum J$ = 28.8 Hz, 1H, H-13a), 1.91 (m, $\sum J$ = 37.0 Hz, 1H, H-13b), 1.75 (s, 3H, H-12), 1.17 (d, *J*_{11,5} = 7.3 Hz, 3H, H-11) ppm, with agreement with the published data.²¹

Methyl (1S,3aR,4S,7S,7aR)-1-([1,1'-biphenyl]-2-ylmethyl)-6,7-dimethyl-3-oxo-4-(2-phenethoxyethyl)-1,2,3,4,7,7a-hexahydro-3aH-isoindole-3a-carboxylate (23). By following the slightly modified general procedure, the cross-coupling reaction was carried out with Fe(acac)₃ (30 mg, 86.2 μmol), **19** (40 mg, 86.6 μmol) in dry THF (0.5 mL), TMEDA (13 μL, 86.6 μmol), 2-biphenylmagnesium bromide (1.33 mL, 0.5 M in 2-MeTHF, 664 μmol) and dry THF (0.8 mL) for 24 h. **Removal of the unreacted starting material 19:** after the solvent evaporation, the crude product was treated with a small piece of sodium (approx. 3 × 3 × 3 mm) and dry MeOH (2 mL) and the resulting reaction mixture was stirred at RT under argon atmosphere for 24 h. Then, the mixture was quenched with saturated aqueous NH₄Cl (0.5 ml) and concentrated under reduced pressure. The residue was taken up in H₂O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried (MgSO₄) and the solvent was evaporated *in vacuo*. FC (eluent: EtOAc in hexane 0% to 70%, the product elutes at 50%) followed by preparative HPLC (eluent: EtOAc in hexane 0% to 50%, the product elutes at 40%) furnished compound **23** (13 mg, 28%) as a yellowish dense oil. ¹H NMR (400 MHz, CDCl₃) δ 7.46–7.14 (m, 14H, Ph, biphenyl), 5.36 (m, $\sum J$ = 11.7 Hz, 1H, H-7), 5.23 (s, 1H, NH), 3.72 (s, 3H, OCH₃), 3.64 (dt, *J*_{gem} = 9.4, *J*_{15a,16a} = *J*_{15a,16b} = 7.3 Hz, 1H, H-15a), 3.54 (dt, *J*_{gem} = 9.2, *J*_{15b,16a} = *J*_{15b,16b} = 7.2 Hz, 1H, H-15b), 3.47 (m, $\sum J$ = 13.0 Hz, 2H, 2 × H-14), 3.16 (dd, *J*_{gem} = 13.2, *J*_{10a,3} = 3.5 Hz, 1H, H-10a), 2.84 (t, *J*_{16,15a} = *J*_{16,15a} = 7.2 Hz, 2H, 2 × H-16), 2.78 (dt, *J*_{3,4} = 10.2, *J*_{3,10a} = *J*_{3,10b} = 3.7 Hz, 1H, H-3), 2.59 (m, $\sum J$ = 12.9 Hz, 1H, H-8), 2.51 (dd, *J*_{gem} = 13.3, *J*_{10b,3} = 10.5 Hz, 1H, H-10b), 2.34–2.19 (m, 2H, H-4,5), 2.07 (m, $\sum J$ = 36.5 Hz, 1H, H-13a), 1.81 (m, $\sum J$ = 58.0 Hz, 1H, H-13b), 1.47 (s, 3H, H-12), 0.49 (d, *J*_{11,5} = 7.3 Hz, 3H, H-11) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 173.42 (C-1), 173.24 (COOCH₃), 142.21 (C-2'), 141.58 (C-7'), 139.36 (C-*i*-Ph), 139.32 (C-6), 134.91 (C-1'), 130.83 (C-3'), 130.75 (C-6'), 129.29 (C-8',12'), 129.05 (C-*o*-Ph), 128.70 (C-9',11'), 128.29 (C-*m*-Ph), 127.95 (C-4'/C-5'), 127.39 (C-10'), 127.20 (C-4'/C-5'), 126.48 (C-7), 126.06 (C-*p*-Ph), 71.42 (C-15), 69.97 (C-14), 60.27 (C-9), 54.72 (C-4), 54.28 (C-3), 52.79 (COOCH₃), 42.52 (C-10), 36.42 (C-8,16), 34.11 (C-5), 29.80 (C-13), 20.07 (C-12), 12.97 (C-11) ppm. **HRMS** (ESI) *m/z* calcd

for C₃₅H₃₉O₄NNa [M + Na]⁺ 560.2771; found 560.2775. [α]_D = –1.9° (c 0.173; CHCl₃).

Methyl (1S,3aR,4S,7S,7aR)-6,7-dimethyl-3-oxo-4-(2-phenethoxyethyl)-1-(4-phenoxybenzyl)-1,2,3,4,7,7a-hexahydro-3aH-isoindole-3a-carboxylate (24). By following the slightly modified general procedure, the cross-coupling reaction was carried out with Fe(acac)₃ (30 mg, 86.2 μmol), **19** (40 mg, 86.6 μmol) in dry THF (0.5 mL), TMEDA (13 μL, 86.6 μmol), 4-phenoxyphenylmagnesium bromide (1.33 mL, 0.5 M in THF, 664 μmol) and dry THF (1 mL) for 4.5 h. FC (eluent: EtOAc in hexane 0% to 75%, the product elutes at 40% EtOAc) followed by column chromatography (eluent: EtOAc in hexane 0% to 60%, the product elutes at 40%) furnished mixture of product **24** and starting material **19**. **Removal of the unreacted starting material 19:** after the solvent evaporation, the crude product was treated with a small piece of sodium (approx. 3 × 3 × 3 mm) and dry MeOH (2 mL) and the resulting reaction mixture was stirred at RT under argon atmosphere for 68 h. Then, the mixture was quenched with saturated aqueous NH₄Cl (0.5 ml) and concentrated under reduced pressure. The residue was taken up in H₂O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried (MgSO₄) and the solvent was evaporated *in vacuo*. The column chromatography (eluent: EtOAc in hexane 0% to 80%, the product elutes at 40% EtOAc) furnished compound **24** (12 mg, 25%) as a yellowish dense oil. ¹H NMR (400 MHz, CDCl₃) δ 7.34 (m, $\sum J$ = 16.2 Hz, 2H, 2 × H-7'), 7.29–7.16 (m, 5H, H-*o,m,p*-Ph), 7.14–7.08 (m, 3H, 2 × H-2', H-8'), 7.01–6.94 (m, 4H, 2 × H-3',6'), 5.65 (s, 1H, NH), 5.50 (m, $\sum J$ = 8.2 Hz, 1H, H-7), 3.78 (s, 3H, OCH₃), 3.66 (m, $\sum J$ = 16.0 Hz, 1H, H-15a), 3.58 (m, $\sum J$ = 17.1 Hz, 1H, H-15b), 3.53 (m, $\sum J$ = 13.0 Hz, 2H, 2 × H-14), 3.22 (dt, *J*_{3,4} = 9.2, *J*_{3,10a} = *J*_{3,10b} = 4.6 Hz, 1H, H-3), 2.91–2.82 (m, 3H, 2 × H-16, H-10a), 2.72 (m, $\sum J$ = 11.5 Hz, 1H, H-8), 2.62 (dd, *J*_{gem} = 13.6, *J*_{10b,3} = 9.6 Hz, 1H, H-10b), 2.57 (dd, *J*_{4,3} = *J*_{4,5} = 4.5 Hz, 1H, H-4), 2.48 (m, $\sum J$ = 21.8 Hz, 1H, H-5), 2.11 (m, $\sum J$ = 28.9 Hz, 1H, H-13a), 1.92 (dm, *J*_{gem} = 14.1 Hz, 1H, H-13b), 1.75 (s, 3H, H-12), 1.16 (d, *J*_{11,5} = 7.3 Hz, 3H, H-11) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 173.55 (C-1), 173.13 (COOCH₃), 157.10 (C-5'), 156.27 (C-4'), 139.27 (C-*i*-Ph), 138.97 (C-6), 132.17 (C-1'), 130.37 (2 × C-2'), 129.77 (2 × C-7'), 128.96 (C-*o*-Ph), 128.20 (C-*m*-Ph), 126.77 (C-7), 125.98 (C-*p*-Ph), 123.33 (C-8'), 119.30 (2 × C-3'), 118.74 (2 × C-6'), 71.35 (C-15), 69.82 (C-14), 60.24 (C-9), 55.77 (C-3), 53.84 (C-4), 52.76 (COOCH₃), 44.19 (C-10), 36.52 (C-8), 36.34 (C-16), 34.24 (C-5), 29.94 (C-13), 20.31 (C-12), 14.05 (C-11) ppm. **HRMS** (ESI) *m/z* calcd for C₃₅H₃₉O₅NNa [M + Na]⁺ 576.2720; found 576.2722. [α]_D = –15.4° (c 0.158; CHCl₃).

Methyl (1S,3aR,4S,7S,7aR)-1-(4-fluorobenzyl)-6,7-dimethyl-3-oxo-4-(2-phenethoxyethyl)-1,2,3,4,7,7a-hexahydro-3aH-isoindole-3a-carboxylate (25). By following the general procedure, the cross-coupling reaction was carried out with Fe(acac)₃ (76 mg, 215 μmol), **19** (100 mg, 215 μmol) in dry THF (0.5 mL), TMEDA (32 μL, 215 μmol), 4-fluorophenylmagnesium bromide (830 μL, 2 M in Et₂O, 1.66 mmol) and dry and degassed THF (1.5 mL) for 24 h. FC (eluent: EtOAc in hexane 0% to 66%, the product elutes at 40% EtOAc) followed by two preparative



HPLC (eluent: EtOAc in hexane 0% to 100%, the product elutes at 40% EtOAc) furnished compound **25** (15 mg, 15%) as a yellowish dense oil. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.29–7.16 (m, 5H, Ph), 7.12 (m, $\sum J = 15.8$ Hz, 2H, $2 \times \text{H-}o\text{-PhF}$), 7.01 (m, $\sum J = 18.1$ Hz, 2H, $2 \times \text{H-}m\text{-PhF}$), 5.55 (s, 1H, NH), 5.49 (m, $\sum J = 11.3$ Hz, 1H, H-7), 3.76 (s, 3H, OCH_3), 3.67 (dt, $J_{\text{gem}} = 9.3$, $J_{15a,16a} = J_{15a,16b} = 7.2$ Hz, 1H, H-15a), 3.57 (m, $\sum J = 16.0$ Hz, 1H, H-15b), 3.52 (m, $\sum J = 13.6$ Hz, 2H, $2 \times \text{H-}14$), 3.20 (dt, $J_{3,4} = 8.4$, $J_{3,10a} = J_{3,10b} = 4.1$ Hz, 1H, H-3), 2.90–2.81 (m, 3H, $2 \times \text{H-}16$, H-10a), 2.75–2.67 (m, $\sum J = 21.8$ Hz, 1H, H-8), 2.62 (dd, $J_{\text{gem}} = 13.7$, $J_{10b,3} = 9.3$ Hz, 1H, H-10b), 2.55 (t, $J_{4,3} = J_{4,5} = 4.5$ Hz, 1H, H-4), 2.48 (m, $\sum J = 24.1$ Hz, 1H, H-5), 2.09 (m, $\sum J = 36.6$ Hz, 1H, H-13a), 1.91 (dm, $J_{\text{gem}} = 14.0$ Hz, 1H, H-13b), 1.75 (s, 3H, H-12), 1.15 (d, $J_{11,5} = 7.2$ Hz, 3H, H-11) ppm. $^{13}\text{C}\{^{19}\text{F}\}$ NMR (101 MHz, CDCl_3) δ 173.58 (C-1), 173.10 (COOCH_3), 161.89 (C-*p*-PhF), 139.25 (C-*i*-Ph), 138.92 (C-6), 133.01 (C-*i*-PhF), 130.65 (C-*o*-PhF), 128.95 (C-*o*-Ph), 128.20 (C-*m*-Ph), 126.79 (C-7), 125.97 (C-*p*-Ph), 115.72 (C-*m*-PhF), 71.35 (C-15), 69.80 (C-14), 60.18 (C-9), 55.63 (C-3), 53.71 (C-4), 52.74 (COOCH_3), 43.99 (C-10), 36.54 (C-16), 36.32 (C-8), 34.21 (C-5), 29.91 (C-13), 20.27 (C-12), 14.03 (C-11) ppm. $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -116.08 ppm. HRMS (ESI) m/z calcd for $\text{C}_{29}\text{H}_{34}\text{O}_4\text{NFNa}$ [$\text{M} + \text{Na}$] $^+$ 502.2364; found 502.2366. $[\alpha]_{\text{D}} = 0^\circ$ (c 0.160; CHCl_3).

Methyl (1S,3aR,4S,7S,7aR)-6,7-dimethyl-3-oxo-1-(phenanthren-9-ylmethyl)-4-(2-phenethoxyethyl)-1,2,3,4,7,7a-hexahydro-3aH-isoindole-3a-carboxylate (26). By following the general procedure, the cross-coupling reaction was carried out with Fe(acac) $_3$ (38 mg, 108 μmol), **19** (50 mg, 108 μmol) in dry THF (0.5 mL), TMEDA (16 μL , 108 μmol), 9-phenanthrylmagnesium bromide (5.3 mL, 0.16 M in THF, 830 μmol) and dry and degassed THF (1 mL) for 24 h. FC (eluent: EtOAc in hexane 0% to 50%, the product elutes at 40% EtOAc) followed by two preparative HPLC (eluent: EtOAc in hexane 0% to 40%, the product elutes at 40% EtOAc) furnished compound **26** (8 mg, 13%) as a yellowish amorphous solid. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.77 (dd, $J = 7.0$, 2.7 Hz, 1H, H-Phenan), 8.66 (dd, $J = 8.0$, 1.5 Hz, 1H, H-Phenan), 8.02 (dd, $J = 6.8$, 2.8 Hz, 1H, H-Phenan), 7.87 (dd, $J = 7.8$, 1.5 Hz, 1H, H-Phenan), 7.74–7.59 (m, 5H, $5 \times \text{H-Phenan}$), 7.29–7.16 (m, 5H, Ph), 5.51 (s, 1H, NH), 5.46 (m, $\sum J = 8.7$ Hz, 1H, H-7), 3.89 (s, 3H, OCH_3), 3.68 (dt, $J_{\text{gem}} = 9.4$, $J_{15a,16a} = J_{15a,16b} = 7.2$ Hz, 1H, H-15a), 3.61–3.43 (m, 5H, H-3,10a, $2 \times 14,15b$), 3.10 (m, $\sum J = 25.6$ Hz, 1H, H-10b), 2.87 (t, $J_{16,15a} = J_{16,15b} = 7.2$ Hz, 2H, $2 \times \text{H-}16$), 2.77–2.72 (m, 2H, H-4,8), 2.54 (m, $\sum J = 21.9$ Hz, 1H, H-5), 2.13 (m, $\sum J = 32.7$ Hz, 1H, H-13a), 1.92 (dm, $J_{\text{gem}} = 14.1$ Hz, 1H, H-13b), 1.71 (s, 3H, H-12), 1.26 (d, $J_{11,5} = 7.2$ Hz, 3H, H-11) ppm. $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 173.32 (C-1/ COOCH_3), 173.28 (C-1/ COOCH_3), 139.26 (C-*i*-Ph), 138.92 (C-6), 131.64 (C-Phenan), 131.26 (C-Phenan), 131.01 (C-Phenan), 130.49 (C-Phenan), 129.93 (C-Phenan), 128.96 (C-*o*-Ph), 128.36 (CH-Phenan), 128.31 (CH-Phenan), 128.19 (C-*m*-Ph), 127.01 (CH-Phenan), 126.85 (HC-Phenan), 126.77 (C-7), 126.67 (HC-Phenan), 125.97 (C-*p*-Ph), 123.77 (CH-Phenan), 123.64 (CH-Phenan), 122.44 (CH-Phenan), 71.35 (C-15), 69.82 (C-14), 60.27 (C-9), 54.97 (C-4), 53.86 (C-3), 52.86 (COOCH_3), 42.76 (C-10), 36.48 (C-8),

36.33 (C-16), 34.27 (C-5), 29.89 (C-13), 20.19 (C-12), 14.28 (C-11) ppm. HRMS (ESI) m/z calcd for $\text{C}_{37}\text{H}_{39}\text{O}_4\text{NNa}$ [$\text{M} + \text{Na}$] $^+$ 584.2771; found 584.2768. $[\alpha]_{\text{D}} = -25.7^\circ$ (c 0.165; CHCl_3).

Methyl (1S,3aR,4S,7S,7aR)-6,7-dimethyl-1-(naphthalen-2-ylmethyl)-3-oxo-4-(2-phenethoxyethyl)-1,2,3,4,7,7a-hexahydro-3aH-isoindole-3a-carboxylate (27). By following the general procedure, the cross-coupling reaction was carried out with Fe(acac) $_3$ (43 mg, 123 μmol), **19** (57 mg, 123 μmol) in dry THF (0.5 mL), TMEDA (18 μL , 123 μmol), 2-naphthalenylmagnesium bromide (3.26 mL, 0.29 M in THF, 946 μmol) and dry and degassed THF (0.5 mL) for 24 h. FC (eluent: EtOAc in hexane 0% to 50%, the product elutes at 40%) followed by two preparative HPLC (eluent: EtOAc in hexane 0% to 100%, the product elutes at 40%) furnished compound **27** (5 mg, 8%) as a yellowish amorphous solid. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.84–7.78 (m, 3H, Naph-H-4',5',8'), 7.61 (s, 1H, Naph-H-1'), 7.53–7.44 (m, 2H, Naph-H-6',7'), 7.30–7.15 (m, 6H, Naph-H-3', H-*o,m,p*-Ph), 5.50 (m, 2H, NH, H-7), 3.73 (s, 3H, OCH_3), 3.67 (ddd, $J_{\text{gem}} = 9.5$, $J_{15a,16a} = J_{15a,16b} = 7.3$ Hz, 1H, H-15a), 3.57 (m, $\sum J = 16.1$ Hz, 1H, H-15b), 3.52 (m, $\sum J = 13.2$ Hz, 2H, $2 \times \text{H-}14$), 3.32 (ddd, $J_{3,10a} = 9.7$, $J_{3,4} = J_{3,10b} = 3.8$ Hz, 1H, H-3), 3.06 (dd, $J_{\text{gem}} = 13.3$, $J_{10a,3} = 3.6$ Hz, 1H, H-10a), 2.87 (t, $J_{16,15a} = J_{16,15b} = 7.2$ Hz, 2H, $2 \times \text{H-}16$), 2.80 (dd, $J_{\text{gem}} = 13.5$, $J_{10b,3} = 9.8$ Hz, 1H, H-10b), 2.72 (m, $\sum J = 9.4$ Hz, 1H, H-8), 2.64 (t, $J_{4,3} = J_{4,5} = 4.5$ Hz, 1H, H-4), 2.51 (m, $\sum J = 21.5$ Hz, 1H, H-5), 2.11 (dm, $J_{\text{gem}} = 14.5$ Hz, 1H, H-13a), 1.90 (m, $\sum J = 35.5$ Hz, 1H, H-13b), 1.77 (s, 3H, H-12), 1.24 (d, $J_{11,5} = 5.6$ Hz, 3H, H-11) ppm. $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 173.51 (C-1), 173.18 (COOCH_3), 139.26 (C-*i*-Ph), 138.97 (C-6), 134.81 (Naph-C-2'), 133.45 (Naph-C-8a'), 132.35 (Naph-C-4a'), 128.96 (C-*o*-Ph), 128.70 (Naph-CH-4'), 128.20 (C-*m*-Ph), 127.71 (Naph-CH-1'/5'/8'), 127.64 (Naph-CH-1'/5'/8'), 127.53 (Naph-CH-1'/5'/8'), 127.10 (Naph-CH-3'), 126.77 (C-7), 126.41 (Naph-CH-7'), 125.97 (C-*p*-Ph), 125.86 (Naph-CH-6'), 71.34 (C-15), 69.82 (C-14), 60.24 (C-9), 55.64 (C-3), 53.98 (C-4), 52.71 (COOCH_3), 45.13 (C-10), 36.50 (C-8), 36.33 (C-16), 34.30 (C-5), 29.92 (C-13), 20.32 (C-12), 14.15 (C-11) ppm. HRMS (ESI) m/z calcd for $\text{C}_{33}\text{H}_{37}\text{O}_4\text{NNa}$ [$\text{M} + \text{Na}$] $^+$ 534.2615; found 534.2611. $[\alpha]_{\text{D}} = -12.6^\circ$ (c 0.141; CHCl_3).

Methyl (1S,3aR,4S,7S,7aR)-6,7-dimethyl-3-oxo-4-(2-phenethoxyethyl)-1-phenethyl-1,2,3,4,7,7a-hexahydro-3aH-isoindole-3a-carboxylate (28). By following the general procedure, the cross-coupling reaction was carried out with Fe(acac) $_3$ (76 mg, 215 μmol), **19** (100 mg, 215 μmol) in dry THF (0.5 mL), TMEDA (32 μL , 215 μmol), benzylmagnesium chloride (830 μL , 2 M in THF, 1.66 mmol) and dry and degassed THF (1.5 mL) for 24 h. FC (eluent: EtOAc in hexane 0% to 100%, the product elutes at 40%) followed by preparative HPLC (eluent: EtOAc in hexane 0% to 100%, the product elutes at 40% EtOAc) furnished compound **28** (7 mg, 7%) as a yellowish dense oil and a debrominated compound **22** (29 mg, 35%) as a yellowish dense oil. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.33–7.14 (m, 10H, Ph, Bn), 6.04 (s, 1H, NH), 5.49 (p, $J_{7,8} = J_{7,12} = 2.0$ Hz, 1H, H-7), 3.75 (s, 3H, OCH_3), 3.67 (dt, $J_{\text{gem}} = 9.3$, $J_{15a,16a} = J_{15a,16b} = 7.1$ Hz, 1H, H-15a), 3.57 (m, $\sum J = 16.8$ Hz, 1H, H-15b), 3.53 (m, $\sum J = 13.0$ Hz, 2H, $2 \times \text{H-}14$), 2.99 (m, $\sum J = 16.4$ Hz, 1H, H-3), 2.87 (t, $J_{16,15a} = J_{16,15b} = 7.2$ Hz, 2H, $2 \times \text{H-}16$), 2.75–2.67 (m, 2H,



H-8, Bn-CH₂a), 2.57 (ddd, $J_{gem} = 13.9$, $J_{Bn-CH_2b,10a} = 9.2$, $J_{Bn-CH_2b,10b} = 7.3$ Hz, 1H, Bn-CH₂b), 2.47–2.41 (m, 2H, H-4,5), 2.11 (m, $\sum J = 30.9$ Hz, 1H, H-13a), 1.93 (m, $\sum J = 29.6$ Hz, 1H, H-13b), 1.85–1.78 (m, 2H, 2× H-10), 1.65 (dm, $J_{7,12} = 2.5$ Hz, 3H, H-12), 1.08 (d, $J_{11,5} = 7.1$ Hz, 3H, H-11) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 174.09 (C-1), 173.20 (COOCH₃), 140.60 (C-*i*-Bn), 139.26 (C-*i*-Ph), 139.08 (C-6), 128.96 (C-*o*-Ph), 128.62 (C-*m*-Bn), 128.27 (C-*m*-Ph/C-*o*-Bn), 128.20 (C-*m*-Ph/C-*o*-Bn), 126.60 (C-7), 126.29 (C-*p*-Bn), 125.97 (C-*p*-Ph), 71.34 (C-15), 69.86 (C-14), 59.92 (C-9), 54.60 (C-4), 53.57 (C-3), 52.65 (COOCH₃), 40.27 (C-10), 36.47 (C-8), 36.33 (C-16), 34.30 (C-5), 32.54 (Bn-CH₂), 29.98 (C-13), 20.18 (C-12), 14.00 (C-11) ppm. HRMS (ESI) m/z calcd for C₃₀H₃₇O₄NNa [M + Na]⁺ 498.2615; found 498.2611. $[\alpha]_D = +12.3^\circ$ (c 0.153; CHCl₃).

Methyl (1*S*,3*aR*,4*S*,7*S*,7*aR*)-1,6,7-trimethyl-3-oxo-4-(2-phenethoxyethyl)-1,2,3,4,7,7*a*-hexahydro-3*aH*-isoindole-3*a*-carboxylate (22). ¹H NMR (400 MHz, CDCl₃) δ 7.29–7.15 (m, 5H, Ph), 5.97 (s, 1H, NH), 5.50 (m, $\sum J = 11.3$ Hz, 1H, H-7), 3.77 (s, 3H, OCH₃), 3.67 (dt, $J_{gem} = 9.3$, $J_{15a,16a} = J_{15a,16b} = 7.2$ Hz, 1H, H-15a), 3.61–3.50 (m, 3H, H-14,15b), 3.15 (m, $\sum J = 23.3$ Hz, 1H, H-3), 2.87 (t, $J_{16,15a} = J_{16,15b} = 7.2$ Hz, 2H, H-16), 2.71 (m, $\sum J = 13.6$ Hz, 1H, H-8), 2.44 (m, $\sum J = 23.3$ Hz, 1H, H-5), 2.38 (t, $J_{4,3} = J_{4,5} = 4.5$ Hz, 1H, H-4), 2.13 (dm, $J_{gem} = 14.0$ Hz, 1H, H-13a), 1.88 (dm, $J_{gem} = 14.0$ Hz, 1H, H-13b), 1.73 (s, 3H, CH₃-12), 1.22 (d, $J_{10,3} = 6.2$ Hz, 3H, CH₃-10), 1.15 (d, $J_{11,5} = 7.2$ Hz, 3H, CH₃-11) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 173.87 (C-1), 173.27 (COOCH₃), 139.27 (C-*i*-Ph), 139.01 (C-6), 128.95 (C-*o*-Ph), 128.19 (C-*m*-Ph), 126.56 (C-7), 125.96 (C-*p*-Ph), 71.32 (C-15), 69.89 (C-14), 60.40 (C-9), 56.37 (C-4), 52.66 (COOCH₃), 49.80 (C-3), 36.34 (C-16), 36.26 (C-8), 34.14 (C-5), 30.03 (C-13), 24.51 (C-10), 20.29 (C-12), 14.01 (C-11) ppm. HRMS (ESI) m/z calcd for C₂₃H₃₁O₄NNa [M + Na]⁺ 408.2145; found 408.2144. $[\alpha]_D = +70.3^\circ$ (c 0.158; CHCl₃).

Cultivation of cell lines

Human BLM (derived from melanoma) and MRC-5 (lung fibroblasts; Merck, USA) cells were utilized in this study to assess the cytotoxicity of the prepared compounds *in vitro*. Both cell lines were kept at the exponential phase of growth and regularly passaged using trypsin–EDTA solution. BLM cells were cultured in high-glucose DMEM supplemented with 10% (v/v) fetal bovine serum (FBS; Merck, USA) and stable L-glutamine. MRC-5 were maintained in MEM + 10% (v/v) FBS, stable L-glutamine, and 1% (v/v) non-essential amino acids. The cells were incubated at 37 °C, 5% CO₂ in the atmosphere and 95% humidity.

Compound cytotoxicity measurement

Cytotoxicity of the evaluated compounds was determined using a colorimetric WST-1 viability assay (Merck, USA) similarly as reported in ref. 21. The amount of 5000 BLM and MRC-5 cells were seeded in 100 μ L of cell media into wells of flat-bottom 96-well plates and incubated at standard conditions for 24 h. Then, the cells were treated with a concentration series of the measured compounds diluted in 100 μ L of cell media. This was added into the wells with cells and incu-

bated for 72 h. After that, the viability of BLM and MRC-5 cells was determined using WST-1 (4% v/v solution in FluoroBrite DMEM) after 2 h incubation, at which formazan absorption was assessed spectrophotometrically at 450 nm (reference wavelength at 650 nm) by a UV-vis spectrophotometer (Bio-Rad, USA). Untreated cells and cells treated only with a vehicle (DMSO) served as controls. The experiment occurred in at least three independent measurements each of which consisted of three technical replicates. The data were plotted as dose-response curves from which the half-maximal inhibitory concentrations (IC₅₀) were calculated by AAT Bioquest.

Conclusions

This study explores the potential of transition metal-mediated reactions for introducing aryl groups at position 10 of the cytochalasan scaffold as a tool for modular modifications at this position. The methodology was optimised using 2-pyrrolidones as model starting materials. An excellent yield was obtained using a Co(acac)₃-catalyzed reaction with PhMgBr and TMEDA as a ligand when using *N*-MOM protected 5-(bromomethyl)-2-pyrrolidone 4 as the starting material. However, unprotected 5-(bromomethyl)-2-pyrrolidone 7 was only successfully arylated with PhMgBr using stoichiometric amounts of Fe(acac)₃ and TMEDA. Although arylations with the corresponding cytochalasan-like bromide suffered from partial debromination of the starting material, we identified conditions that predominantly led to the formation of arylated products. This methodology was applied to the synthesis of six new aryl- and benzyl-substituted cytochalasan analogues 23–28. These compounds exhibited comparable or lower cytotoxic activity compared to known cytochalasan analogues lacking the macrocyclic moiety.

Our results demonstrate a viable method for introducing aryl groups of different sizes and substitutions at position 10 during the late stages of cytochalasan analogue synthesis, more than 30 years after the arylation was first proposed. It is the first example of a late-stage modification in this position and due to its modular character, it holds promise for conducting further SAR studies on cytochalasans. It could contribute to a deeper understanding of the role of aryl groups in their interaction with actin and other protein targets.

Conflicts of interest

No conflict of interest to declare.

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