Palladium-catalyzed pseudo-domino cyclizations
An easy entry toward polycondensed pyrrolidone derivatives

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Dedicated to Professor Jean-Pierre Genêt on the occasion of his 60th birthday

Abstract

A new type I palladium-catalyzed pseudo-domino process is developed, in which a single Pd-based catalytic system promotes two mechanistically unrelated, sequential catalytic cycles in chronologically distinct order. Suitable precursors undergo an allylic alkylation and a Heck coupling in sequence, affording polycondensed pyrrolidone derivatives. Depending on the starting precursors, intra/inter or doubly intramolecular processes can be obtained. The allylic alkylation process takes place always very smoothly. On the other hand, the Heck coupling turns out to be rather difficult either when the process is intermolecular, or when an intramolecular process generates polycondensed structures featuring three fused bonds connected to a common carbon atom. In such difficult cases, use of the Herrmann–Beller phosphapalladacycle allowed to catalyze the coupling. This study demonstrates also that allylic alkylations can be catalyzed by the Herrmann–Beller phosphapalladacycle.
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1. Introduction

The research in the field of domino reactions is attracting considerable attention in synthetic organic chemistry since it enables the rapid assembly of complex molecules in one-pot processes [1]. In this context, very elegant examples of transition metal-catalyzed domino processes wherein a single catalytic cycle entails several sequential bond transformations have been recently reviewed [2].

On the other hand, multistep palladium-catalyzed processes featuring sequential and mechanistically independent catalytic cycles have been so far much less studied [3]. Albeit synthetically interesting and mechanistically intriguing, their success cannot be given for granted owing to possible undesired sequential enchaining or incompatibilities among the different catalytic cycles. In order to better appreciate these processes, we recently proposed to conceptually differentiate these transformations from the more traditional domino transformations, by classifying them as "transition metal-catalyzed pseudo-domino" processes (TM-PDOM). Further subdivision into type I or type II process is also possible, if a single multipurpose catalytic system ("M"), or mutually compatible catalytic systems of different nature ("M1, M2, etc.") are respectively involved (Fig. 1).

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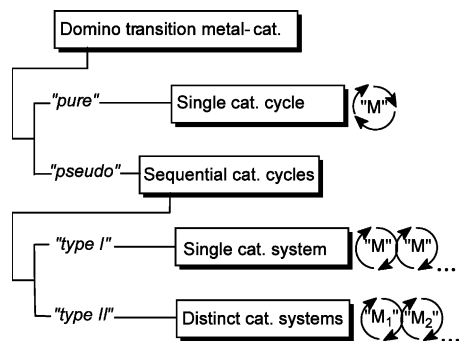
Fig. 1. Classification of domino transition metal-catalyzed processes.

2. Results and discussion

### 2.1. The intra/inter-molecular process

We started our investigations in multistep one-pot palladium-catalyzed processes by studying the behavior of mixtures of amide **1** and aryl bromides in the presence of palladium catalysts. After considerable experimentation, we could observe the expected allylic alkylation [4]/ Heck coupling pseudo-domino sequence (Pd-PDOM type I), which led to (*E*)-3-β-styryl pyrrolidone derivatives **2a**–**2e** [5]. Despite the overall positive outcome, acceptable results for the latter step were obtained only when the Herrmann–Beller phosphapalladacycle [6,7] was used as the catalyst. Such a result was mechanistically very interesting, since it demonstrated for the first time that allylic alkylations can be efficiently catalyzed by this palladacycle, a catalyst whose mechanism in the Heck coupling has been long debated [8]. On the other hand, complete arylation of the vinyl chain was never achieved, and the high temperature required brought about demethoxycarbonylation of the product (Scheme 1).
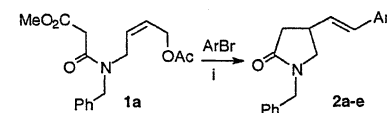
Entry	Ar	product	yield (%)
1	3-MeOC$_6$H$_4$	**2a**	58
2	4-MeOC$_6$H$_4$	**2b**	38
3	C$_6$H$_5$	**2c**	54
4	3-MeCOC$_6$H$_4$	**2d**	59
5	4-MeCOC$_6$H$_4$	**2e**	60

i : NaH (1.2 equiv.), ArBr (1.4 equiv.), AcONa (1.1 equiv.), Herrmann–Beller cat. (0.05 equiv.), Me$_2$NAc, 140°C, 22–47h. 1-Benzyl-4-vinyl-pyrrolidin-2-one was often obtained as a secondary product (see experimental).

Scheme 1. Pd-PDOM intramolecular allylic alkylation/intermolecular Heck coupling.
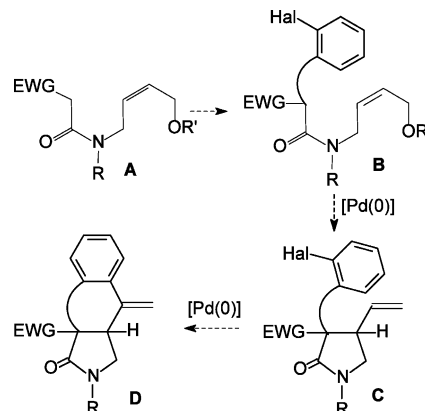
Scheme 2. Construction of *o*-haloarylated precursor **B** and its expected doubly intramolecular Pd-PDOM transformation.
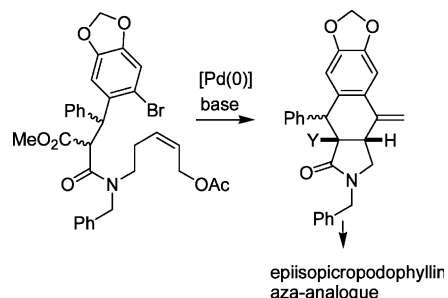
2.2. The doubly intramolecular process

As an extension of the above study, we decided to investigate next a doubly intramolecular variant of the Pd-PDOM process. We judged, in fact, that such a modification could enable the one-pot construction of synthetically interesting complex polycyclic structures. In particular, we envisaged to convert amide **A** into the *o*-haloaryl derivative **B**, in the hope that the transiently generated 3-vinyl pyrrolidone **C** could directly undergo an unimolecular Heck process, to generate the polycyclic structure **D** (Scheme 2).

Indeed, such a strategy has been successfully exploited by us in the synthesis of an aza-analogue of epiisopicropodophyllin, the C-3 epimer of podophyllotoxin (Scheme 3) [9].

In order to gain more information on the scope of above Pd-PDOM process, we then decided to study the double cyclization sequence as a function of the nature of the group stabilizing the α-amide anion, as well as of the structure of the allylic moiety in the precursor.

Accordingly, amide **1a** was alkylated with *o*-bromobenzyl bromide, and the newly generated amide **3a** was submitted to cyclization (Scheme 4). In contrast to the intra/inter-molecular version, we soon realized that the Herrmann–Beller phosphapalladacycle was no more essential for the Heck process. Indeed, deprotonation

epiisopicropodophyllin aza-analogue

Scheme 3. Doubly intramolecular Pd-PDOM process affording an epiisopicropodophyllin aza-analogue.

of amide **3a** with NaH in DMF, followed by treatment with (Pd(OAc)$_2$/1,2-bis-(diphenylphosphino)ethane (dppe)) and appropriate heating gave rise smoothly to the *trans* and *cis* double cyclization products *trans*-**4** and *cis*-**4** in a 38:62 ratio.

Interesting to note, this double intramolecular process is much faster than the previously described intra/inter-molecular approach. Such a result suggests that the rate-determining step of the catalytic cycle associated with the intermolecular Heck coupling is likely to be the carbopalladation step, and not the oxidative addition step [10]. It should also be pointed out that the allylic alkylation process is the stereodetermining step, and its selectivity is directly transposed into the diastereomeric ratio of the final tricyclic product. Furthermore, the *trans/cis* ratios observed in this step are expected to reflect a kinetic control. In fact, the allylation processes are usually irreversible processes, and, in contrast to related cyclizations previously studied by us [4,11], the resulting 2,2-disubstituted-3-vinyl pyrrolidones cannot undergo equilibration via enolization.

The same cyclization protocol has been successively applied to the two *o*-bromobenzylated amides **3b** and **3c**, having respectively a nitrile and a phenysulfonyl group as carbanion-stabilizing moieties. In the event, the cyano derivative afforded the expected tricyclic structures *trans*-**4b** and *cis*-**4b** in a 89:11 ratio, whereas the sulfonylated derivative gave *cis*-**4c** as the only detectable diastereomer.

Unequivocal assignment of the stereochemistry at the ring junction was obtained via a combination of spectroscopic and diffraction methods. Indeed, in all the three cases studied, only one diastereomer of the couple showed a nil allylic coupling constant value ($^4J_{ab} = 0$ Hz) in the ^{1}H-NMR spectrum. Furthermore, the same type of isomer was always associated with a larger chemical shift difference between the two sets of peaks pertaining to the *N*-benzylic AB system, as compared with the other isomer. Such a behavior clearly suggested that a correlation exists between the above
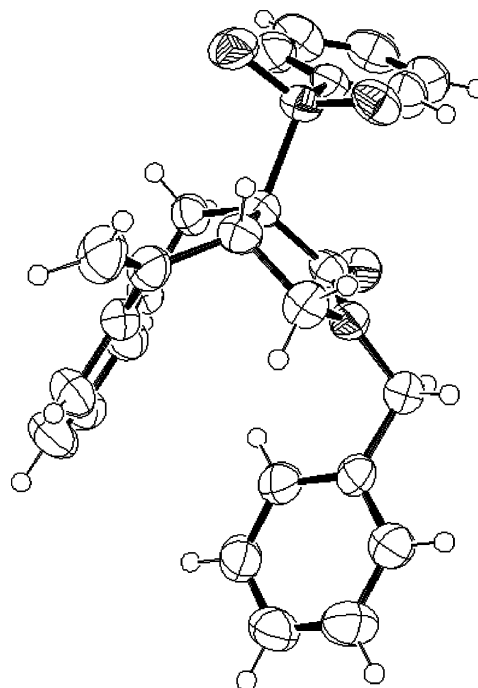

Fig. 2. ORTEP drawing of the tricyclic amide *cis*-**4c**.

spectroscopic trends and the relative configuration of the ring junction. On the other hand, the X-ray structure of the crystalline sulfone derivative *cis*-**4c** (Fig. 2), which in turn possessed a nil allylic coupling constant value, unveiled a *cis* stereochemistry at the ring junction. Accordingly, we could tentatively correlate the isomers featuring $^4J_{ab} = 0$ Hz to the *cis* configured products, and those having $J \neq 0$ Hz to the *trans* ones (Table 1).

Inspection of Table 1 reveals that the *trans*:*cis* ratio of the tricyclic products is directly dependent on the steric requirements of the carbanion-stabilizing group (EWG). More precisely, the bigger the stabilizing group, the higher the resulting *cis*:*trans* ratio. Such a trend may be cautiously rationalized on steric grounds, according to the differential destabilizing eclipsing interactions ensuing at the transition state level, between the internal
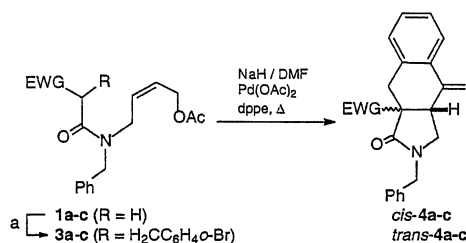

Entry	EWG [b]	3	yield 3 (%)	4	T °C	time (h)	*trans*-4 : *cis*-4 [c]	yield (%) of 4 (*t* + *c*)
1	CO$_2$Me	3a	90	4a	110	1	38 : 62	81
2	CN	3b	86	4b	120	1	89 : 11	82
3	SO$_2$Ph	3c	64	4c	140	2	≤ 2 : ≥ 98	82

a) NaH / DMF, 100°C, 1h, *o*-BrC$_6$H$_4$CH$_2$Br. b) EWG = **a**: CO$_2$Me; **b**: CN; **c**: SO$_2$Ph. c) Determined on the ^{1}H NMR spectra of the crude reaction mixtures.

Scheme 4. Formation of precursors **3a**–**3c** and their doubly intramolecular Pd-PDOM (allylic alkylation/Heck) transformations.
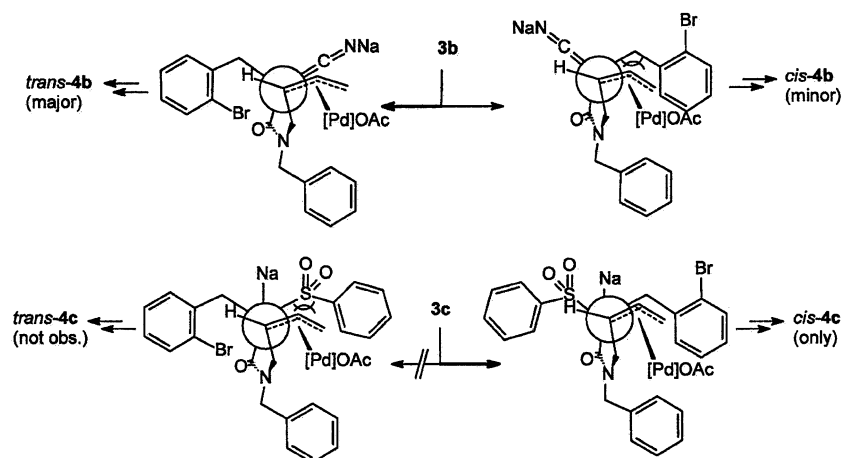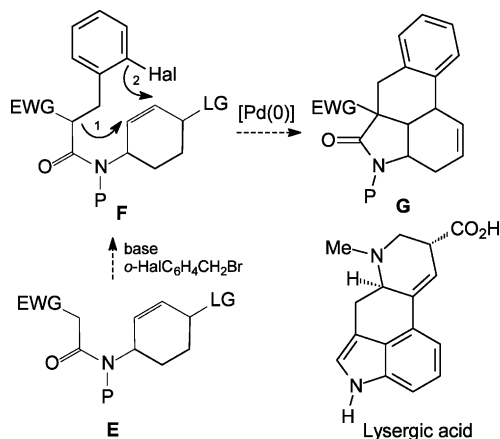
Table 1
J_{ab} constants and relative ppm differences for diagnostic sets of peak
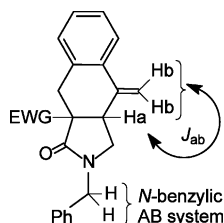
Entry	EWG	Compound	$^4J_{ab}$ (Hz) [a]	AB system [b]
1	MeO$_2$C	trans-**4a**	1.85	0.24
2	MeO$_2$C	cis-**4a**	0	0.64
3	NC	trans-**4b**	1.90	0.13
4	NC	cis-**4b**	0	0.61
5	PhO$_2$S	cis-**4c**	0	–

[a] Average value.
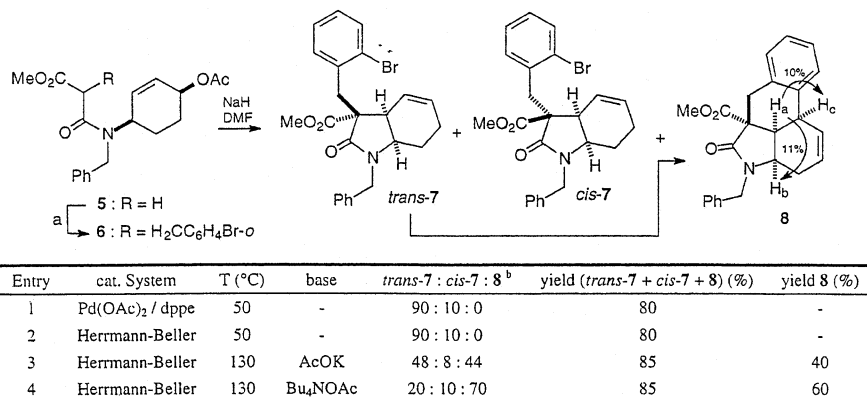[b] Relative ppm difference between the two sets of peaks.

C=C portion of the allyl fragment and, either the EWG, or the bromobenzylic residue [12]. Accordingly, the stereochemical outcome may be accounted for, assuming that the internal C=C portion of the allyl fragment will preferentially eclipse the less sterically demanding group. Hence, the *trans* product will be favored when the bromobenzylic residue is bulkier than the EWG (nitrile derivative), whereas the preference reverts when the steric requirements of EWG become overwhelming (sulfone derivative) (see Scheme 5).

With the aim of obtaining synthetically more complex polycondensed structures, we next envisaged to extend our cyclization studies to precursors wherein the allylic moiety is incorporated into a cyclic structure. Thus, for example, eliciting of the above-described pseudo-domino process on the new precursor **F**, obtainable via *o*-halobenzylation of amide **E**, was anticipated to afford

Scheme 6. Expected Pd-PDOM doubly intramolecular process on the cyclic precursor **F** and comparison with lysergic acid structure.

the polycondensed structure **G**, a compound featuring the lysergic acid backbone (Scheme 6).

Accordingly, the new *o*-bromobenzylated amide **6**, in turn obtained from the cyclic precursor **5** [13], was prepared and tested for cyclization (Scheme 7). Deprotonation of **5** with NaH at 0 °C followed by treatment with *o*-bromobenzyl bromide in DMF at 100 °C, gave uneventfully the expected precursor in 95% yield. Then, treatment of **6** with NaH at 0 °C in DMF, followed by addition of the catalytic system (Pd(OAc)$_2$/dppe) and heating at 50 °C, gave the allylic alkylation product **7** in a 90:10 *trans:cis* ratio as the only new product (entry 1). The same result was obtained when the Herrmann– Beller catalyst was used in place of the (Pd(OAc)$_2$/ dppe) system, thereby confirming the ability of this catalyst to catalyze the allylic alkylation reaction (entry 2). On the other hand, when the latter reaction was performed at 130 °C, and in the presence of AcOK, formation of the desired tetracyclic product **8** as the only

Scheme 5. Rationalization of the stereochemical outcome in the Pd(0)-catalyzed intramolecular allylic alkylation of amides **3a**–**3c**.

Entry	cat. System	T (°C)	base	trans-7 : cis-7 : 8 [b]	yield (trans-7 + cis-7 + 8) (%)	yield 8 (%)
1	Pd(OAc)$_2$ / dppe	50	-	90 : 10 : 0	80	-
2	Herrmann-Beller	50	-	90 : 10 : 0	80	-
3	Herrmann-Beller	130	AcOK	48 : 8 : 44	85	40
4	Herrmann-Beller	130	Bu$_4$NOAc	20 : 10 : 70	85	60

a) Conversion of **5** to **6**: NaH, o-BrC$_6$H$_4$CH$_2$Br, DMF, 100°C (95%). b) Determined on the ^{1}H NMR spectra of the crude reaction mixtures.

Scheme 7. Preparation of the cyclic precursor **6** and its Pd(0)-catalyzed cyclization.

diastereomer, together with *trans*-**7** and *cis*-**7**, was observed in a 44:48:8 ratio, respectively (entry 3). Gratifyingly enough, when AcOK was replaced for Bu$_4$NOAc, so as to mimic Jeffery conditions [14], the **8**:*trans*-**7**:*cis*-**7** ratio improved to 70:20:10 and the yield of isolated **8** raised to 60%. The results assembled in Scheme 7 clearly indicate that tetracycle **8** has to originate exclusively from the cyclization of *trans*-**7**, the other diastereomer being too strained to do so. An NOE difference experiment on **8** unequivocally demonstrated the spatial proximity of the three vicinal methine hydrogen atoms H$_a$, H$_b$, and H$_c$, thereby confirming the stereochemical assignment of this compound, and consequently of its precursor (*trans*-**7**) and the epimer of the latter (*cis*-**7**).

Attainment of the tetracyclic structure **8** as the only diastereomer in a satisfactory yield was a remarkable result, due to the intrinsic high diastereoselectivity of the in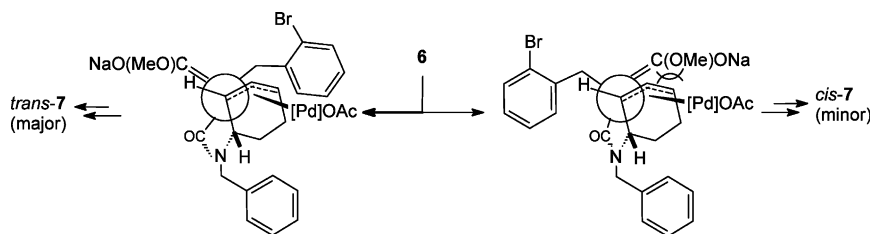tramolecular allylic alkylation in combination with the experimentally observed intramolecular Heck coupling of the only major isomer. It has also to be pointed out that while the former Pd-PDOM process features an achiral precursor (**3**), which is transformed into **4** with the concomitant generation of two vicinal stereogenic centers (internal diastereoselection), the precursor of the latter process (**6**) bears a stereogenic center, capable of governing the allylic alkylation step (diastereofacial selection). Furthermore, the presence of the pre-existing ring structure in precursor **6** forces the *syn* regiospecific dehydropalladation, during the Heck coupling, so as to generate an additional stereogenic center in the final product (Scheme 8, compare sequence **3**→**H**→**I**→**L**→**4** with **6**→**M**→**N**→**8**).

Coming back to the allylic alkylation step, the same steric grounds as invoked in the former process may account for the observed stereochemical result. However, in this latter case uncertainty on configuration of the η^3-allyl fragment is no more present, owing to its
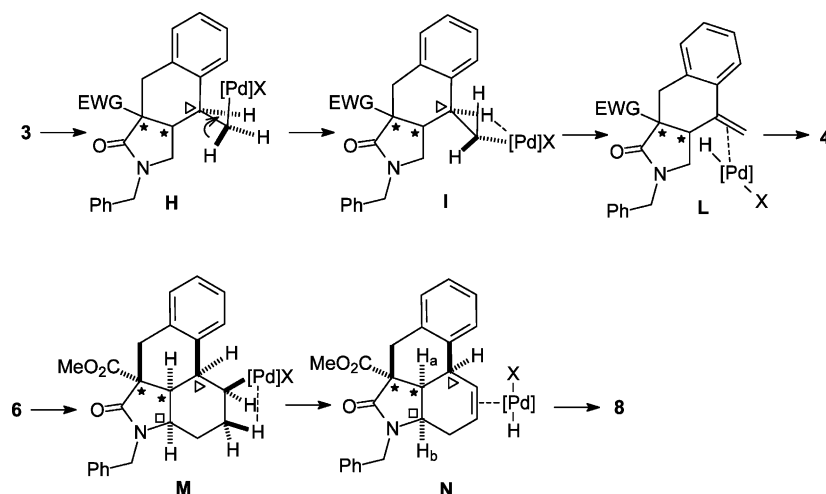
Scheme 8. Comparison of the dehydropalladation processes during transformations **3**→**4** and **6**→**8**. Key for the stereogenic centers: (*) generated during the allylic alkylation; (△) generated during the Heck coupling; (□) pre-existing in the substrate.

Scheme 9. Rationalization of the stereochemical outcome in the Pd(0)-catalyzed intramolecular allylic alkylation of amide **6**.

incorporation into the six-membered structure. As a matter of fact, cyclization of **6** appears to be more selective than that of the corresponding acyclic methoxycarbonylated precursor **4a** (Scheme 9, compare also entry 1 in Scheme 4 with entries 1 or 2 in Scheme 7).

3. Concluding remarks

This study has shown a new type I palladium-catalyzed pseudo-domino process, wherein a single Pd-based catalytic system is able to promote two mechanistically distinct, successive catalytic cycles in a precise chronological order. Suitable precursors were synthesized and submitted to sequential intra/inter or doubly intramolecular allylic alkylation/Heck coupling sequences, thereby obtaining differently substituted pyrrolidone derivatives. While the allylic alkylation step took place always very easily, the Heck coupling turned out to be rather hard, either when it was intermolecular, or when polycondensed structures bearing three fused bonds connected to a common carbon atom were generated. In such difficult cases, the Herrmann–Beller phosphapalladacycle allowed to catalyze the Heck coupling and, at the same time, the preceding allylic alkylation step. Further work is currently underway to explore applications of the above methodology as well as other TM-PDOM processes.

4. Experimental

4.1. General

All reactions were conducted under dried nitrogen or argon atmosphere using oven-dried glassware. For air- and/or water-sensitive reactions, glassware was flame-dried and then allowed cooling under argon or dried nitrogen atmosphere before use. All solvents were purified and distilled according to standard methods. Chromatographic purifications were conducted using 40–63 or 15–40 μm silica gel. All NMR spectra were recorded in CDCl₃. Elemental analyses were carried out with accepted tolerance of ±0.3 units on carbon (C), hydrogen (H) and nitrogen (N). All compounds were

isolated as oils unless otherwise specified, and their purities were determined to be >95% by NMR analysis.

4.2. General procedure for the synthesis 1-benzyl-4-[(E)-2-(3-methoxy-phenyl)-vinyl]-pyrrolidin-2-one (2a), 1-benzyl-4-[(E)-2-(4-methoxy-phenyl)-vinyl]-pyrrolidin-2-one (2b), 1-benzyl-4-[(E)-2-phenyl-vinyl]-pyrrolidin-2-one (2c), 1-benzyl-4-[(E)-2-(3-acetyl-phenyl)-vinyl]-pyrrolidin-2-one (2d), 1-benzyl-4-[(E)-2-(4-acetyl-phenyl)-vinyl]-pyrrolidin-2-one (2e)

To a solution of the acyclic precursor **1** (0.2 mmol) in dry Me₂NAc (5 ml), under nitrogen atmosphere, cooled in a water-ice bath, NaH (60% dispersion in mineral oil) (0.24 mmol) was added and the solution was stirred at r.t. for 20 min. Then, the proper aryl-halide (3-bromoanisole for **2a**, 4-bromoanisole for **2b**, bromobenzene for **2c**, 3-bromoacetophenone for **2d**, 4-bromoacetophenone for **2e**) (0.28 mmol), anhydrous AcONa (0.22 mmol) and trans-di-(μ-acetate)-bis[o-(di-o-tolylphosphine)benzyl]-dipalladium(II) (Herrmann–Beller catalyst) (0.02 mmol) were added in this order with stirring. The resulting mixture was brought to 140 °C for the appropriate time (**2a**: 47 h, **2b**: 50 h, **2c**: 31 h, **2d** and **3d**: 22 h), then a 25 wt.% aqueous solution of NH₄Cl (40 ml) was added and the aqueous phase was extracted with Et₂O (3 × 10 ml). The collected organic phases were dried and the solvent was removed in vacuo. Flash chromatography (hexanes:AcOEt) gave the pure compounds as oils (**2a**, 58%; **2b**, 38%; **2c**, 54%; **2d**, 59%; **2e**, 60%). 1-Benzyl-4-vinyl-pyrrolidin-2-one (see below for the characterization) was also obtained as an undesired byproduct in 36, 42, and 30% during the preparation of **2a**, **2b**, and **2c**, respectively. **2a**: ¹H-NMR (CDCl₃, 200 MHz): δ 2.41 (dd, 1H, $J = 16.8, 8.1$ Hz), 2.71 (dd, 1H, $J = 16.5, 8.1$ Hz), 3.22–3.03 (2H), 3.44 (m, 1H), 3.80 (s, 3H), 4.48 (s, 2H), 6.10 (dd, 1H, $J_{trans} = 15.7, 7.3$ Hz), 6.38 (d, 1H, $J_{trans} = 15.7$ Hz), 6.91–6.75 (3H), 7.40–7.15 (6H) ppm. ¹³C-NMR (CDCl₃, 200 MHz): δ 35.5, 37.7, 46.5, 52.0, 55.2, 111.5, 113.3, 118.8, 127.6, 127.7, 128.2, 128.8, 129.6, 131.0, 136.3, 138.1, 159.9, 173.4 ppm. IR (CDCl₃): 3034, 2930, 1674 cm⁻¹. MS (EI) m/z (%): 307 [22], 186 [2], 173 [15], 160 [39], 159 [46], 158 [9], 91 [100]. Anal. Calcd. for C₂₀H₂₁NO₂: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.06; H, 6.61; N, 4.47%. **2b**: ¹H-NMR (CDCl₃, 200 MHz): δ

2.39 (dd, 1H, $J = 16.5$, 8.1 Hz), 2.69 (dd, 1H, $J = 16.5$, 8.1 Hz), 3.18–3.05 (2H), 3.43 (m, 1H), 3.79 (s, 3H), 4.47 (s, 2H), 5.96 (dd, 1H, $J_{trans} = 15.8$, $J = 7.3$ Hz), 6.35 (d, 1H, $J_{trans} = 15.8$ Hz), 6.83 (d, 2H, $J_{ortho} = 8.8$ Hz), 7.39–7.18 (7H) ppm. ^{13}C-NMR (CDCl$_3$, 50.3 MHz): δ 35.6, 37.9, 46.5, 52.2, 55.3, 114.0, 127.3, 127.7, 127.8, 128.2, 128.7, 129.4, 130.4, 136.4, 159.3, 174.0 ppm. IR (CDCl$_3$): 3036, 2932, 1673 cm^{-1}. MS (EI) m/z (%): 308 [M+H$^+$, 8], 307 [26], 292 [2], 173 [7], 160 [69], 159 [46], 145 [18], 144 [20], 134 [29], 121 [26], 120 [16], 119 [5], 91 [100]. **2c**: ^{1}H-NMR (CDCl$_3$, 200 MHz): δ 2.40 (dd, 1H, $J = 16.9$, 8.1 Hz), 2.70 (dd, 1H, $J = 16.1$, 8.1 Hz), 3.22–3.05 (2H), 3.45 (m, 1H), 4.47 (s, 2H), 6.10 (dd, 1H, $J_{trans} = 15.7$, 7.4 Hz), 6.41 (d, 1H, $J_{trans} = 15.7$ Hz), 7.39–7.17 (10H) ppm. ^{13}C-NMR (CDCl$_3$, 50.3 MHz): δ 35.9, 37.2, 46.5, 52.0, 115.7, 126.2, 127.7, 128.2, 128.7, 128.8, 130.0, 131.1, 136.6, 138.5, 173.9 ppm. IR (CDCl$_3$): 3033, 2930, 2858, 1669 cm^{-1}. MS (EI) m/z (%): 278 [6], 277 [27], 131 [10], 130 [81], 129 [90], 128 [36], 115 [39], 91 [100]. Anal. Calcd. for C$_{19}$H$_{19}$NO: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.16; H, 6.78; N, 4.96%. **2d**: ^{1}H-NMR (CDCl$_3$, 200 MHz): δ 2.41 (dd, 1H, $J = 16.9$, 8.1 Hz), 2.59 (s, 3H), 2.71 (dd, 1H, $J = 16.9$, 8.5 Hz), 3.24–3.07 (2H), 3.45 (m, 1H), 4.48 (s, 2H), 6.20 (dd, 1H, $J_{trans} = 15.8$, $J = 7.4$ Hz), 6.45 (d, 1H, $J_{trans} = 15.8$ Hz), 7.51–7.22 (7H), 7.88–7.77 (2H) ppm. ^{13}C-NMR (CDCl$_3$, 50.3 MHz): δ 26.7, 35.5, 37.6, 46.6, 51.9, 125.8, 127.5, 127.7, 128.2, 128.8, 128.9, 130.2, 130.7, 131.5, 136.3, 137.1, 137.5, 173.7, 198.1 ppm. IR (CDCl$_3$): 3034, 2928, 1690, 1674 cm^{-1}. MS (EI) m/z (%): 320 [12], 319 [46], 306 [1], 305 [4], 278 [11], 277 [37], 201 [16], 129 [88], 128 [85], 127 [38], 120 [89], 91 [100]. **2e**: ^{1}H-NMR (CDCl$_3$, 200 MHz): δ 2.42 (dd, 1H, $J = 16.5$, 8.1 Hz), 2.57 (s, 3H), 2.72 (dd, 1H, $J = 16.8$, 8.1 Hz), 3.25–3.06 (2H), 3.46 (m, 1H), 4.47 (s, 2H), 6.24 (dd, 1H, $J_{trans} = 16.1$ Hz, $J = 7.0$ Hz), 6.44 (d, 1H, $J_{trans} = 16.1$ Hz), 7.41–7.22 (7H), 7.88 (d, 2H, $J_{ortho} = 8.4$ Hz) ppm. ^{13}C-NMR (CDCl$_3$, 50.3 MHz): δ 26.6, 35.6, 37.6, 46.6, 51.8, 126.3, 127.7, 128.2, 128.7, 128.8, 130.2, 133.0, 136.1, 136.3, 141.2, 173.6, 197.5 ppm. IR (CDCl$_3$): 3035, 2925, 2857, 1690, 1675 cm^{-1}. MS (EI) m/z (%): 320 [8], 319 [40], 318 [5], 304 [1], 172 [11], 146 [9], 130 [11], 129 [84], 128 [65], 120 [46], 104 [13], 91 [100]. Anal. Calcd. for C$_{21}$H$_{21}$NO$_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.84; H, 6.61; N, 4.27%. 1-Benzyl-4-vinyl-pyrrolidin-2-one: ^{1}H-NMR (CDCl$_3$, 200 MHz): δ 2.32 (dd, 1H, $J = 16.5$, 8.4 Hz), 2.62 (dd, 1H, $J = 16.5$, 8.4 Hz), 3.07–2.86 (2H), 3.37 (m, 1H), 4.44 (system AB, 2H), 5.00 (d, 1H, $J_{cis} = 2.9$ Hz), 5.08 (d, 1H, $J_{trans} = 9.5$ Hz), 5.76 (m, 1H), 7.39–7.17 (5H) ppm. ^{13}C-NMR (CDCl$_3$, 50.3 MHz): δ 35.9, 37.3, 46.6, 51.8, 115.8, 127.7, 128.2, 128.7, 136.3, 138.5, 174.0 ppm. IR (CDCl$_3$): 3069, 3033, 2929, 2857, 1673 cm^{-1}. MS (EI) m/z (%): 202 [13], 201 [69], 146 [19], 146 [20], 104 [19], 103 [22], 91 [100]. Anal. Calcd. for C$_{13}$H$_{15}$NO: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.48; H, 7.39; N, 6.79%.

4.3. General procedure for the synthesis of (±)-(Z)-4-{benzyl-[2-(2-bromo-benzyl)-2-methoxycarbonyl-acetyl]-amino}-but-2-enyl-acetate (3a), (±)-(Z)-4-{benzyl-[2-(2-bromo-benzyl)-2-cyano-acetyl]-amino}-but-2-enyl-acetate (3b), (±)-(Z)-4-{benzyl-[2-(2-bromo-benzyl)-2-phenylsulfonyl-acetyl]-amino}-but-2-enyl-acetate (3c)

To a solution of the acyclic substrate (**1a**, **1b**, or **1c**) (1.50 mmol) in dry DMF (6 ml), under nitrogen atmosphere, cooled in a water-ice bath, NaH (60% dispersion in mineral oil) (1.80 mmol) was added and the solution was stirred at r.t. for 20 min. 2-Bromobenzyl bromide (1.80 mmol) as solution in dry DMF (2 ml) was added and reaction mixture was heated at 100 °C for 1 h. A 25 wt.% aqueous solution of NH$_4$Cl (50 ml) was added and the aqueous phase was extracted with Et$_2$O (3 × 10 ml). The collected organic phases were dried and the solvent was removed in vacuo. Flash chromatography (hexanes:AcOEt) gave the pure products as oils (**3a**, 90%; **3b**, 64%; and **3c**, 86%). **3a**: ^{1}H-NMR (CDCl$_3$, 200 MHz): δ 1.98 (s, 3H, 51%), 2.00 (s, 3H, 49%), 3.53–3.29 (2H), 3.69 (s, 3H, 51%), 3.75 (s, 3H, 49%), 3.86 (d, 2H, 49%, $J = 5.8$ Hz), 3.98 (d, 2H, 51%, $J = 6.6$ Hz), 4.17 (m, 1H), 4.63–4.33 (4H), 5.69–5.04 (2H), 7.53–6.86 (9H) ppm. ^{13}C-NMR (CDCl$_3$, 50.3 MHz): δ 20.8, 35.6, 35.7, 42.9, 44.4, 47.6, 47.7, 48.8, 50.6, 52.6, 59.6, 59.8, 124.5, 124.7, 126.4, 127.0, 127.2, 127.4, 127.6, 127.6, 127.7, 128.0, 128.5, 128.7, 128.8, 129.0, 129.4, 132.5, 132.6, 132.7, 132.8, 135.8, 136.6, 137.3, 137.4, 168.3, 169.5, 169.5, 170.69 ppm. IR (CHCl$_3$): 3005, 2957, 1736, 1642 cm^{-1}. MS (EI) m/z (%): 490 [0.2], 488 [0.2], 430 [9], 428 [14], 409 [13], 408 [10], 171 [28], 169 [29], 91 [100]. Anal. Calcd. for C$_{25}$H$_{28}$BrNO$_5$: C, 59.77; H, 5.62; N, 2.79. Found: C, 59.59; H, 5.47; N, 2.61%. **3b**: ^{1}H-NMR (CDCl$_3$, 200 MHz): δ 1.94 (s, 1H, 45%), 1.96 (s, 1H, 55%), 3.53–3.21 (2H), 4.23–3.88 (3H), 4.59–4.37 (4H), 5.78–5.23 (2H), 7.54–7.00 (9H) ppm. ^{13}C-NMR (CDCl$_3$, 50.3 MHz): δ 20.7, 20.8, 34.3, 34.4, 36.6, 43.9, 44.6, 49.6, 50.8, 59.3, 59.6, 116.5, 116.7, 124.3, 124.4, 126.2, 127.9, 128.0, 128.0, 128.1, 128.1, 128.2, 128.6, 128.8, 129.2, 129.6, 132.5, 132.9, 135.1, 135.2, 135.3, 136.0, 164.5, 164.6, 170.5, 170.6 ppm. MS (EI) m/z (%): 397 [27], 395 [30], 343 [10], 341 [12], 261 [100]. IR (CH$_2$Cl$_2$): 3017, 2957, 2260, 1731, 1668 cm^{-1}. Anal. Calcd. for C$_{24}$H$_{25}$BrN$_2$O$_3$: C, 61.41; H, 5.37; N, 5.97. Found: C, 61.23; H, 5.19; N, 6.02%. **3c**: ^{1}H-NMR (CDCl$_3$, 200 MHz): δ 1.94 (s, 1H, 45%), 1.98 (s, 1H, 55%), 3.77–3.21 (3H), 4.29–3.95 (2H), 4.54–4.31 (3H), 4.79–4.62 (2H), 5.68–5.29 (2H), 6.53 (m, 1H), 7.68–6.92 (11H), 7.97–7.81 (2H) ppm. ^{13}C-NMR (CDCl$_3$, 50.3 MHz): δ 20.8, 34.7, 34.9, 43.7, 44.8, 49.6, 50.8, 59.6, 59.7, 65.0, 65.1, 124.4, 124.6, 126.0, 127.1, 127.5, 127.6, 127.8, 128.0, 128.5, 128.9, 129.0, 129.1, 129.1, 129.2, 129.8, 129.9, 132.5, 132.9, 133.1, 134.4, 134.9, 134.9, 135.4, 136.1, 136.8, 163.9, 164.1, 170.5, 170.6 ppm. MS

(EI) m/z (%): 512 [3.6], 510 [5.2], 370 [7.2], 368 [8.4], 91 [100], 77 [40]. IR (CH$_2$Cl$_2$): 3070, 3005, 2946, 1734, 1661 cm^{-1}. Anal. Calcd. for C$_{29}$H$_{30}$BrNO$_5$S: C, 59.59; H, 5.17; N, 2.40. Found: C, 59.68; H, 5.23; N, 2.60%.

4.4. General procedure for the synthesis of (±)-(9aS,3aS)-2-benzyl-9-methylene-3-oxo-1,2,3,4,9,9a-hexahydro-benzo[f]isoindole-3a-carboxylic acid methyl ester (cis-**4a**), (±)-(9aS,3aR)-2-benzyl-9-methylene-3-oxo-1,2,3,4,9,9a-hexahydro-benzo[f]isoindole-3a-carboxylic acid methyl ester (trans-**4a**), (±)-(9aS,3aS)-2-benzyl-9-methylene-3-oxo-1,2,3,4,9,9a-hexahydro-benzo[f]isoindole-3a-carbonitrile (cis-**4b**), (±)-(9aS,3aR)-2-benzyl-9-methylene-3-oxo-1,2,3,4,9,9a-hexahydro-benzo[f]isoindole-3a-carbonitrile (trans-**4b**), (±)-(9aS,3aS)-9a-benzenesulfonyl-2-benzyl-4-methylene-2,3,3a,4,9,9a-hexahydro-benzo[f]isoindol-1-one (cis-**4c**)

To a solution of the acyclic substrate (**3a**, **3b**, or **3c**) (0.25 mmol) in dry DMF (2 ml), under argon atmosphere, cooled in a water-ice bath, NaH (60% dispersion in mineral oil) (0.28 mmol) was added and the solution was stirred at r.t. for 20 min. In a separate flask, Pd(OAc)$_2$ (0.013 mmol) and dppe (0.025 mmol) were dissolved in dry DMF (1 ml). The previously preformed enolate was transferred under argon atmosphere to the thus formed palladium(0) complex, and the resulting mixture was stirred at the proper temperature for the proper time (see Scheme 4). A 25 wt.% aqueous solution of NH$_4$Cl (30 ml) was added and the aqueous phase was extracted with Et$_2$O (3 × 10 ml). The collected organic phases were dried and the solvent removed in vacuo. Flash chromatography (hexanes:AcOEt) gave the pure compounds. (cis-**4a**, 49% and trans-**4a**, 32%; cis-**4b**, 9% and trans-**4b**, 73%; cis-**4c**, 82%). cis-**4a**: ^{1}H-NMR (CDCl$_3$, 200 MHz): δ 2.85 (m, 1H), 3.08 (part of AB system, d, 1H), 3.36 (part of AB system, d, 1H), 3.73 (2H), 3.80 (s, 3H), 4.00 (part of AB system, d, 1H), 4.64 (part of AB system, d, 1H), 5.04 (s, 1H), 5.25 (s, 1H), 6.64–6.59 (2H), 7.31–7.10 (7H) ppm. ^{13}C-NMR (CDCl$_3$, 50.3 MHz): δ 32.7, 42.5, 46.5, 52.1, 52.9, 57.1, 112.9, 125.5, 127.3, 128.6, 128.6, 134.5, 135.4, 136.3, 145.1, 171.2, 171.9 ppm. MS (EI) m/z (%): 347 [40], 288 [88], 141 [42], 91 [100]. IR (CH$_2$Cl$_2$): 3030, 2955, 2926, 1739, 1691 cm^{-1}; Anal. Calcd. for C$_{22}$H$_{21}$NO$_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 75.96; H, 6.00; N, 4.12%. trans-**4a**: ^{1}H-NMR (CDCl$_3$, 200 MHz): δ 3.08 (part of AB system, d, 1H), 3.17 (m, 1H), 3.36 (dd, 1H, $J = 8.8$, 6.6 Hz), 3.51 (s, 3H), 3.70 (part of AB system, d, 1H), 3.87 (dd, 1H, $J = 10$, 9.1 Hz), 4.48 (part of AB system, d, 1H), 4.72 (part of AB system, d, 1H), 4.79 (d, 1H, $J = 1.9$ Hz), 5.57 (d, 1H, $J = 1.8$ Hz), 7.38–7.15 (8H), 7.58 (m, 1H) ppm. ^{13}C-NMR (CDCl$_3$, 50.3 MHz): δ 29.7, 35.4, 47.0, 41.2, 52.3, 56.6, 106.1, 124.3, 126.3, 127.8, 128.2, 128.6, 128.7,

130.2, 133.9, 135.3, 136.1, 140.2, 169.6, 171.8 ppm. MS (EI) m/z (%): 347 [13], 288 [38], 155 [70], 91 [100]. IR (CH$_2$Cl$_2$): 3028, 2946, 1740, 1693 cm^{-1}. m.p. 106–108 °C. cis-**4b**: ^{1}H-NMR (CDCl$_3$, 200 MHz): δ 2.88 (dd, 1H, $J = 9.2$, 3.3 Hz), 3.11 (part of AB system, d, 1H), 3.39 (part of AB system, d, 1H), 3.82–3.63 (2H), 4.05 (part of AB system, d, 1H), 4.66 (part of AB system, d, 1H), 5.13 (s, 1H), 5.40 (s, 1H), 6.76–6.65 (m, 1H), 7.39–7.16 (8H) ppm. ^{13}C-NMR (CDCl$_3$, 50.3 MHz): δ 29.7, 34.4, 42.8, 47.0, 51.1, 114.2, 119.6, 125.8, 127.5, 127.8, 128.2, 128.6, 128.8, 129.0, 131.8, 134.6, 135.4, 142.4, 167.5 ppm. MS (EI) m/z (%): 314 [23], 166 [7], 91 [100]. IR (CH$_2$Cl$_2$): 3049, 2926, 2854, 2242, 1708 cm^{-1}. trans-**4b**: ^{1}H-NMR (CDCl$_3$, 200 MHz): δ 3.05–2.96 (m, 1H), 3.23 (part of AB system, d, 1H), 3.72–3.42 (2H), 3.54 (part of AB system, d, 1H), 4.53 (part of AB system, d, 1H), 4.66 (part of AB system, d, 1H), 4.91 (d, 1H, $J = 2.2$ Hz), 5.78 (d, 1H, $J = 1.8$ Hz), 7.43–7.16 (8H), 7.73–7.64 (1H) ppm. ^{13}C-NMR (CDCl$_3$, 50.3 MHz): δ 34.9, 46.6, 46.6, 46.9, 47.3, 108,9, 116.5, 124.8, 127.5, 128.0, 128.2, 129.1, 129.4, 130.5, 131.6, 133.1, 135.3, 138.5, 167.8 ppm. MS (EI) m/z (%): 314 [42], 223 [3], 166 [10], 91 [100]. IR (CH$_2$Cl$_2$): 3032, 2929, 2854, 2236, 1709 cm^{-1}. Anal. Calcd. for C$_{21}$H$_{18}$N$_2$O: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.06; H, 5.63; N, 8.90%. cis-**4c**: ^{1}H-NMR (CDCl$_3$, 200 MHz): δ 2.75 (part of AB system, 1H), 3.08 (s, 2H), 3.68 (t, 1H, $J = 9.6$ Hz), 3.94 (part of AB system, 1H), 4.27 (part of AB system, 1H), 4.59 (part of AB system, 1H), 5.23 (s, 1H), 5.27 (s, 1H), 6.47 (2H), 7.24–7.15 (7H), 7.69–7.48 (3H), 8.02 (2H) ppm. ^{13}C-NMR (CDCl$_3$, 50.3 MHz): δ 32.4, 39.2, 46.7, 51.6, 74.0, 114.2, 125.9, 127.1, 127.3, 127.8, 128.4, 128.6, 128.7, 131.0, 132.4, 134.5, 134.9, 135.5, 136.5, 144.5, 167.2 ppm. MS (EI) m/z (%): 429 [1], 288 [48], 196 [9], 91 [100]. IR (CH$_2$Cl$_2$): 3068, 2944, 1703 cm^{-1}. m.p. 172–174 °C. Anal. Calcd. for C$_{26}$H$_{23}$NO$_3$S: C, 72.70; H, 5.40; N, 3.26. Found: C, 72.68; H, 5.36; N, 3.17%.

4.5. (±)-cis-N-(4-Acetoxy-cyclohex-2-enyl)-N-benzyl-2-(2-bromo-benzyl)-malonamic acid methyl ester (**6**)

Solid NaH (10 mg, 0.25 mmol, 60% dispersion in mineral oil) was added to a dry DMF (20 ml) stirred solution of cis-4-acetoxy-1-[benzyl(methylmalonyl)a-mino]-cyclohex-2-ene **5** [13] (86 mg, 0.25 mmol) at 0 °C. After 10 min stirring at this temperature and further 20 min at r.t., a dry DMF (1 ml) solution of o-bromobenzylbromide (63 mg, 0.25) mmol was added to the thus formed enolate, and the resulting mixture was heated at 100 °C for 20 min. Water (10 ml) and ether (50 ml) were then added to the cooled mixture, the organic layer was separated, and the aqueous phase was extracted with ether (3 × 50 ml). The collected organic layers were washed with water (3 × 25 ml), dried over MgSO$_4$ and evaporated under reduced pressure. Flash

chromatography (hexanes:AcOEt) of the crude product gave the bromobenzylated amide **6** (103 mg, 95%). ^{1}H-NMR (CDCl$_3$, 200 MHz) δ 1.40–2.00 (m, 4H), 1.96 (m, 3H), 3.30–3.47 (m, 2H), 3.60 (s, 1H), 3.64 (s, 1H), 3.70 (s, 1H), 3.80–3.90 (m, 0.6H), 4.05–4.36 (m, 1.6H), 4.43–4.74 (m, 0.9H), 4.90–5.4 (m, 2.6H), 5.68–5.95 (m, 1.3H), 6.90–7.00 (m, 1.5H), 7.00–7.30 (m, 6.5H), 7.40–7.60 (m, 1H) ppm. ^{13}C-NMR (CDCl$_3$, 50 MHz) δ 20.3, 22.2, 27.8, 30.7, 36.7, 49.5, 53.0, 53.7, 65.4, 66.1, 125.3, 126.6, 126.7, 127.6, 129.5, 133.4, 134.7, 134.9, 138.2, 138.5, 170.4, 170.5, 170.6 ppm. IR (neat): 1740, 1650, 1430, 1230 cm^{-1}. MS (NH$_3$) (%): 516 [70], 514 [70], 456 [100], 454 [100]. Anal. Calcd. for C$_{26}$H$_{28}$BrNO$_5$: C, 60.71; H, 5.49; N, 2.72. Found: C, 60.56; H, 5.60; N, 2.56%.

4.6. ($\pm$)-trans- and cis-1-Benzyl-3-(2-bromo-benzyl)-2-oxo-2,3,3a,6,7,7a-hexahydro-1H-indole-3-carboxylic acid methyl ester (trans-7) and (cis-7)

Solid NaH (5 mg, 0.12 mmol, 60% dispersion in mineral oil) was added to a water-ice cooled dry DMF (8 ml) solution of **6** (43 mg, 0.1 mmol) under argon atmosphere, and the resulting suspension was stirred for 10 min at 0 °C and further 20 min at r.t. In a separate flask, dppe (4 mg, 0.01 mmol) was added to a dry DMF (2 ml) solution of Pd(OAc)$_2$ (1 mg, 0.005 mmol). The previously generated enolate was then transferred under argon atmosphere to the yellow solution containing the palladium catalyst, and the resulting mixture was heated at 50 °C for a 20-min period. Water (4 ml) and ether (20 ml) were then added to the cooled mixture and the phases were separated. The aqueous phase was extracted with ether (3 × 20 ml), and the collected organic layers were washed with water (3 × 10 ml), dried over MgSO$_4$ and evaporated under reduced pressure. Flash chromatography of the crude product (hexanes:AcOEt) gave *trans*-**7** and *cis*-**7** (27 mg, 80%). Trans-**7**: ^{1}H-NMR (CDCl$_3$, 200 MHz) δ 1.65–2.03 (m, 4H), 3.15 (part of AB system, $J = 17.0$ Hz, 1H), 3.52–3.57 (m, 1H), 3.66 (s, 3H), 3.73 (part of AB system, 1H), 3.90 (AB system, 1H), 3.91 (m, 1H), 5.17 (part of AB system, 1H), 5.28–5.36 (m, 1H), 5.83–5.91 (m, 1H), 6.95–7.40 (m, 8H), 7.55 (d, [3]$J = 3.9$ Hz, 1H) ppm. ^{13}C-NMR (CDCl$_3$, 50 MHz) δ 20.0, 23.5, 37.1, 39.9, 44.6, 53.1, 58,5, 123.2, 125.9, 127.6, 127.9, 128.1, 128.8, 128.9, 129.7, 130.6, 133.1, 136.3, 137.6, 127.7, 136.3, 171.3, 171.7 ppm. IR (neat): 1740, 1690, 1440, 1230 cm^{-1}. MS (CH$_4$): *m/z* 454.1016 (calculated: 454.1018) [M$^+$+1], 456.1012 (calculated: 456.1001) [M$^+$+3]. *cis*-**7**: ^{1}H-NMR (CDCl$_3$, 200 MHz) δ 1.3–2.1 (m, 4H), 2.68 (m, 1H), 3.08–3.15 (m, 1H), 3.51 (part of AB system, 1H), 3.15 (s, 3H), 3.88 (part of AB system, 1H), 3.98 (part of AB system, 1H), 5.14 (part of AB system, 1H), 5.84–5.90 (m, 2H), 6.86–6.90 (m, 2H), 7.00–7.30 (m, 5H), 7.47–7.62 (m, 2H) ppm. ^{13}C-NMR (CDCl$_3$, 50 MHz) δ 22.6, 23.3, 36.3, 44.4, 52.5, 54.1, 61.9, 124.2, 127,5, 127.7,

127.9, 128.6, 128.8, 129.3, 133.0, 133.2, 135.9, 136.3, 171.0, 171.6 ppm. IR (neat): 1740, 1690, 1440, 1220 cm^{-1}. MS (NH$_3$) (%): *m/z* 454 [100], 456 [100].

4.7. ($\pm$)-(3aR,5aR,10bR,10cR)-4-Benzyl-5-oxo-3a,4,5,6,10b,10c-hexahydro-3H-4-aza-acephenanthrylene-5a-carboxylic acid methyl ester (8)

Dry DMF (0.4 ml) was added to *n*-Bu$_4$NOAc (60 mg, 0.2 mmol) and the resulting mixture was degassed twice. After addition of the Herrmann–Beller catalyst (2 mg, 0.0045 mmol), the flask was degassed again and left under argon atmosphere. In a separate flask, NaH (4 mg, 0.1 mmol, 60% dispersion in mineral oil) was added to a water-ice cooled, dry and degassed DMF (4 ml) solution of the precursor **6** (43 mg, 0.1 mmol). After 10 min stirring at 0 °C and further 20 min at r.t., the thus formed enolate was transferred under argon atmosphere into the palladium mixture, and heating was immediately brought to 130 °C. After 1.5 h stirring at 130 °C, the reaction flask was let it cool to r.t., treated with water (10 ml) and ether (20 ml), and the phases were separated. The aqueous layer was extracted with ether (3 × 20 ml), and the collected organic layers were washed with water (3 × 20 ml), dried over MgSO$_4$ and evaporated under reduce pressure. Flash chromatography (hexanes:AcOEt) of the resulting crude product gave the pure tetracycle **8** an oil (22 mg, 60%), plus minor amounts of *trans*-**7** and *cis*-**7**. When AcOK was used instead of *n*-Bu$_4$NOAc, under otherwise identical conditions, tetracycle **8** was obtained in 40% yield. ^{1}H-NMR (CDCl$_3$, 500 MHz) δ 1.94 (m, 1H), 2.22 (m, 1H), 3.07 (dd, $J = 7.2, 9.1$ Hz, 1H), 3.21 (part of AB system, 1H), 3.32 (part of AB system, 1H), 3.50 (d, $J = 6.3$ Hz, 1H), 3.76 (s, 3H), 3.96 (part of AB system, 1H), 4.00 (m, 1H), 4.81 (part of AB system, 1H), 6.00 (m, 1H), 6.15 (m, 1H), 7.07 (m, 2H), 7.17–7.35 (m, 7H) ppm. ^{13}C-NMR (CDCl$_3$, 100 MHz) δ 4.5, 14.0, 20.5, 26.2, 31.0, 42.5, 46.1, 49.0, 146.9, 149.2, 149.3, 150.2, 151.3, 151.7, 156.4, 161.9, 162.2, 164.3 ppm. IR (neat): 1750, 1690, 1450, 1250 cm^{-1}. MS (CH$_4$): *m/z* 374.1751 (calc. 374.1756) [M$^+$+1].

4.8. Crystal data for cis-4c

C$_{26}$H$_{23}$NO$_3$S, $M = 429.51$, orthorhombic, space group *Pbca*, $a = 16.362(5)$ Å, $b = 12.570(5)$ Å, $c = 20.852(5)$ Å, $V = 4289(2)$ Å^3, $Z = 8$, $F(0\,0\,0) = 1808$, $\mu = 1.568$ mm^{-1}, $D_c = 1.330$ g cm^{-3}. Data set, consisting of 3655 ($2\theta_{max} = 120°$) reflections, was collected on a P4 Siemens X-ray diffractometer using the (Cu–K$_\alpha$) radiation ($\lambda = 1.5418$ Å) for the cell parameter determination and data collection. The intensities of two standard reflections were monitored during data collection to check the stability of the crystal; no loss of intensity was recognized. The integrated intensities,

measured at room temperature (293 K) using the $\theta/2\theta$ scan mode, were corrected for Lorentz and polarization effects [15]. The structure was solved by direct methods of SIR97 [16] and refined using the full-matrix least-squares on F^2 provided by SHELXL97 [17]. Anisotropic thermal parameters were used for all the non-hydrogen atoms. The hydrogen atoms of the phenyl rings were assigned in calculated positions, while the others were localized in final difference Fourier map. The final R index was 0.0422 for reflections having $I > 2\sigma(I)$ and 0.0560 for all data.

5. Supplementary material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 209018 for compound *cis*-**4**. Copies of this information may be obtained free of charge from The Director, CCDC, 12, Union Road, Cambridge CB2 1EZ, UK [Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk].

Acknowledgements

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