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Stereoselective Synthesis of Chiral Polycyclic Indolic Architectures through Pd^0-Catalyzed Tandem Deprotection/Cyclization of Tetrahydro-β-carbolines on Allenes

Valérian Gobé and Xavier Guinchard*[a]

Abstract: Enantioenriched *N*-allyl tetrahydro-β-carbolines were prepared by chiral phosphoric acid-catalyzed Pictet–Spengler reactions. The compounds undergo Pd^0-catalyzed cyclizations through a tandem deprotection/cyclization process. The regioselectivity of the attack is controlled by the chain length and by the substitution pattern of the allene function. Products resulting from 5-*exo*- or 6-*exo*-attack were obtained with diastereoisomeric ratio up to 95:5. Azepinopyrrido[3,4-*b*]indoles were obtained by 7-*endo*-cyclizations.

Introduction

Indole alkaloids display structural richness and a broad range of biological activities, rendering them attractive targets for both synthetic and biological purposes.[1] Some typical patterns frequently encountered in such structures define privileged scaffolds that are likely to provide success in the discovery of novel bioactive compounds.[2] Chemists' creativity has led to many strategies for indole synthesis and functionalization[2–3] but there is still an avenue for the discovery of novel scaffolds. The indolo[2,3-*a*]quinolizidine moiety is found in hundreds of natural products and holds a good position in chemist's efforts towards the development of bioactive compounds.[4] The vast majority of natural products featuring the indolo[2,3-*a*]quinolizidine moiety presents a cycle D substituted on positions 1, 2, and 3, generally fused with an additional cycle.[5] In contrast, their 4-substituted congeners are encountered less frequently. (−)-Tangutorine,[6] (−)-normalindine,[7] (−)-cadamine,[8] (−)-manadomanzamines,[9] or (−)-phoebegrandine E[10] are representative natural products of this family (Figure 1). Few total syntheses of such natural products have been reported, with the exception of normalindine,[11] demonstrating the challenge of enantio- and diastereoselective synthesis of such scaffolds.

The synthesis of indolo[2,3-*a*]quinolizidine-containing compounds often relies on a diastereoselective Pictet–Spengler reaction.[12] Over the past few years, Jacobsen, List, Hiemstra, and Wang have made several breakthroughs in this domain by developing Brønsted acid catalyzed enantioselective Pictet–Spengler reactions by using either chiral thioureas[13] or chiral phosphoric acids.[14] Thioureas catalyze Pictet–Spengler reactions with concomitant *N*-acylations[13a] and necessitate the use of highly electron-rich tryptamines if *N*-acylation is to be avoided.[13b] This drawback was addressed recently by Seidel, through the use of a conjugate-base-stabilized thiourea, leading to tetrahydro-β-carbolines in excellent enantiomeric excess (*ee*). This method is mostly limited to aromatic aldehydes.[15] On the other hand, chiral phosphoric acids, when applied to *gem*-diester tryptamines[14a] or *N*-protected tryptamines[14b–d] afford good conversion and *ee* values. In most cases, the tryptamine protecting group must be removed prior to further functionalization, unless it has been conveniently designed to be involved in further steps.[2,16] These methodologies have afforded elegant syntheses of enantioenriched polycyclic architectures.[17]

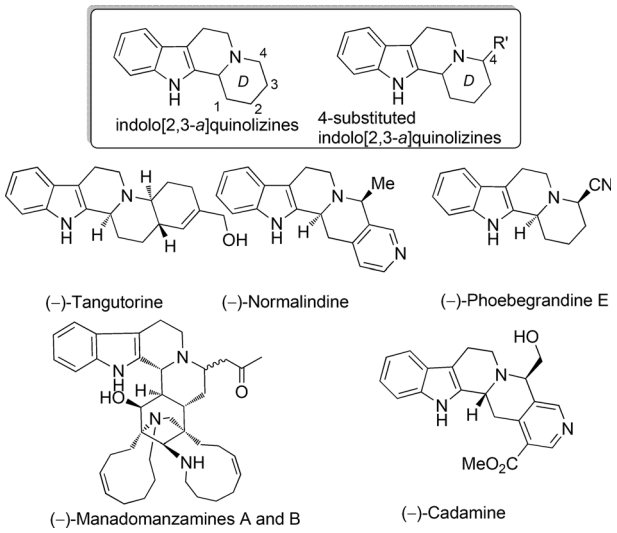

Figure 1. Natural products featuring an indolo[2,3-*a*]quinolizidine skeleton with substituent at the 4-position.

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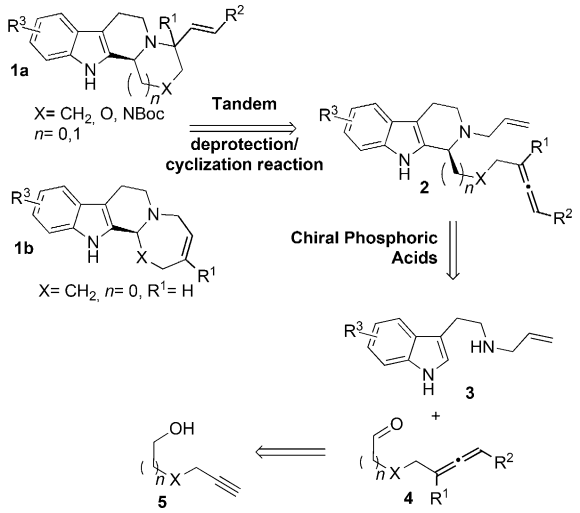


Scheme 1. Synthetic strategy.

We recently described the synthesis of enantioenriched 4-vinyl substituted indolo[2,3*a*]quinolizidines **1a** (>93% *ee*) through a direct palladium-catalyzed tandem deprotection/cyclization from *N*-allyl tetrahydro-β-carbolines **2** (Scheme 1).[18] In this work, the *N*-allyl protecting group of **3** was chosen for its compatibility with the asymmetric Pictet–Spengler reaction catalyzed by chiral phosphoric acids and in the perspective of a one-pot deprotection/cyclization reaction sequence. In this paper, we wish to report on the chemistry developed by using these palladium-catalyzed cyclizations. In particular, we describe the synthesis of highly functionalized chiral heterocycles bearing quaternary stereogenic centers **1a** and heterocycles **1b**, resulting from a novel, regioselective mode of cyclization. The chemistry was extended to 1,3-disubstituted allenes, resulting in the formation of vinyl substituted derivatives **1a** ($R^2 \neq H$). The results of mechanistic studies are presented that provide information on the reaction mechanism of this tandem cyclization process.

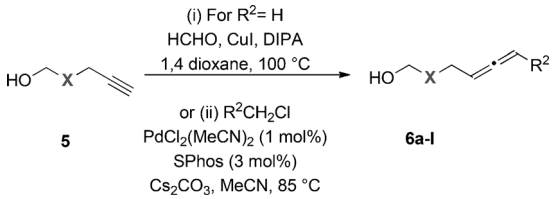
Results and Discussion

Synthesis of Allenaldehydes 4

We initiated this study with the synthesis of a range of allenaldehydes **4**. Numerous methods are available for the construction of the allene function,[19] among which we selected those using an alkyne as starting material, because of the ready availability of 1,*n*-alkynols (see the Supporting Information). Crabbe homologation[20] was used to convert 1,5-, 1,6-, or 1,7-alkynols into terminal allenes **6**, by using the convenient protocol developed by Ma[21] (Table 1, entries 1–5). Allenols **6a**–**e** were obtained in moderate yields that are typical for this type of classical chemical transformation (50–71%).

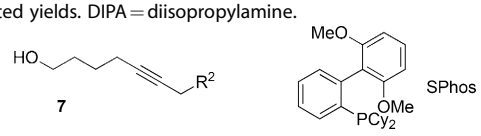
The Heck alkynylation developed by Buchwald[22,23] has been applied here to prepare 7-arylhepta-5,6-dienals in good yields by reaction of alkynes with benzyl chloride and $[Pd(SPhos)_2]$ complex under basic conditions. The reaction conditions were applied to a range of alkynes (Table 1, entries 6–12). The reaction of 4-pentyn-1-ol or 5-hexyn-1-ol furnished allenes **6f** and **6g** in 81 and 75% yields, respectively (Table 1, entries 6–7). Aryl groups bearing halides were used and we found that, surprisingly, whereas *para*-fluorobenzyl chloride led to the allene in 84% yield, the *m*-Br and *p*-Cl analogues were inefficient in this reaction (Table 1, entries 8–9). The electron-rich 4-methoxybenzyl chloride afforded allene **6j** in 57% yield (Table 1, entry 10). Notably, the use of 2-(chloromethyl)pyridine and 2-(prop-2-yn-1-yloxy)ethanol failed to provide the corresponding allene (Table 1, entries 11–12). As reported,[22] allenes **6f**–**h** are often obtained as a mixture with their alkyne precursors **7f**–**h**. In most cases, the allenes can be separated from the alkynes by column chromatography. Interestingly, the allene **6j** did not contain the corresponding alkyne **7j**, although the yield was moderate. Both methods reported in Table 1 are compatible with a free hydroxyl group, thus saving protection/deprotection steps.

Table 1. Synthesis of allenols **6a–l**.



Entry	Conditions	X	R^2	Yield [%][a]
1	i	CH_2CH_2	H	**6a**, 68
2	i	CH_2	H	**6b**, 51
3	i	$CH_2CH_2CH_2$	H	**6c**, 70
4	i	CH_2O	H	**6d**, 50
5	i	$CH_2N(Boc)$	H	**6e**, 55
6	ii	CH_2	Ph	**6f**, 81
7	ii	CH_2CH_2	Ph	**6g**/**7g**, 75 (79:21)
8	ii	CH_2CH_2	*p*-FC_6H_4	**6h**/**7h**, 84 (80:20)
9	ii	CH_2CH_2	*m*-BrC_6H_4 *p*-ClC_6H_4	**6i**–**i'**, 0
10	ii	CH_2CH_2	*p*-$MeOC_6H_4$	**6j**, 57
11	ii	CH_2CH_2	2-pyridine	**6k**, 0
12	ii	CH_2O	Ph	**6l**, 0

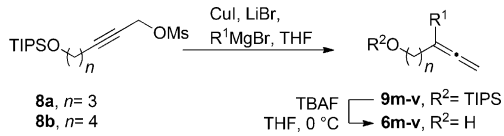
[a] Isolated yields. DIPA = diisopropylamine.



gem-Disubstituted allenes **6m**–**v** were then prepared in two steps. Addition of cuprate reagents to propargylic mesylates **8a**–**b** afforded silylethers **9m**–**v**,[24] which, upon deprotection with fluoride ions,[25] secured the formation of allenols **6m**–**v**. Numerous Grignard reagents could be used successfully with both protected 4-pentynol **8a** and 5-hexynol **8b**, furnishing 1,5- and 1,6-allenols (Table 2). We found that both aliphatic and aromatic groups could be introduced successfully through the corresponding Grignard reagents, including electron-rich (Table 2, entry 9) and halogenated aryl groups (Table 2, entry 10).

Allenols **6a**–**v** were then submitted to Swern oxidation,[26] which furnished the corresponding allenals **4a**–**v** in mostly

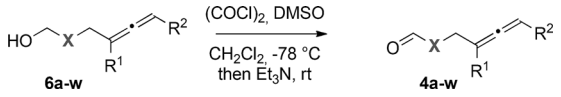
Table 2. Synthesis of *gem*-disubstituted allenols **6m–v**.



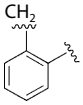
8a, *n*= 3
8b, *n*= 4

Entry	*n*	R^1	Yield of **9** [%][a]	Yield of **6** [%]
1	4	Me	**9m**, 96	**6m**, 94
2	3	Me	**9n**, 88	**6n**, 93
3	4	*i*Pr	**9o**, 86	**6o**, 90
4	3	*i*Pr	**9p**, 87	**6p**, 96
5	4	Ph	**9q**, 83	**6q**, 99
6	3	Ph	**9r**, 69	**6r**, 90
7	4	allyl	**9s**, 82	**6s**, 72
8	3	*t*Bu	**9t**, 92	**6t**, 100
9	3	*p*-$MeOC_6H_4$	**9u**, 100	**6u**, 87
10	3	*p*-ClC_6H_4	**9v**, 100	**6v**, 80

Table 3. Swern oxidation of allenols **6** to allenaldehydes **4**.



6a-w **4a-w**

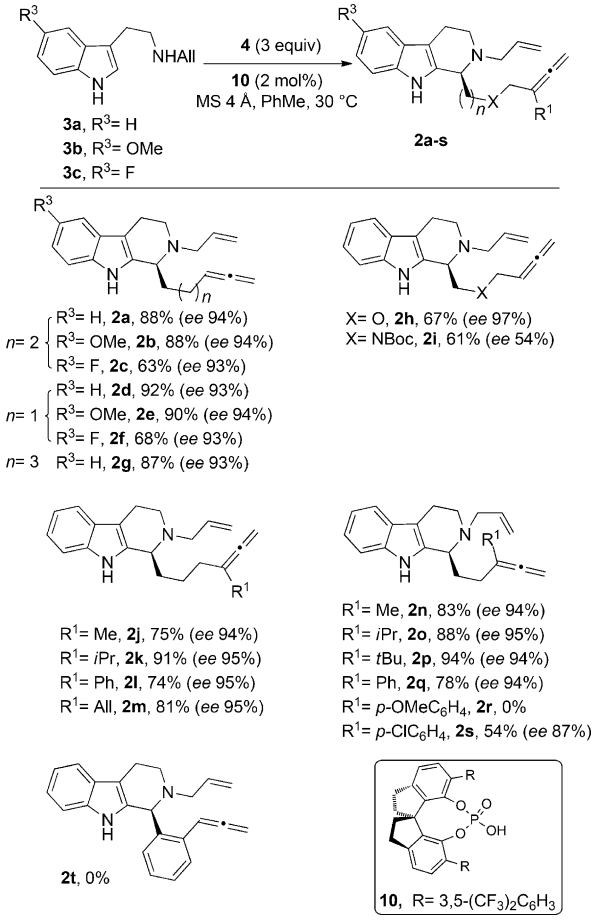
Entry	X	R^1	R^2	Yield of **4** [%][a]
1	CH_2CH_2	H	H	**4a**, 90
2	CH_2	H	H	**4b**, 83
3	$CH_2CH_2CH_2$	H	H	**4c**, 89
4	CH_2O	H	H	**4d**, 61
5	CH_2N(Boc)	H	H	**4e**, 88
6	CH_2	H	Ph	**4f**, 52
7	CH_2CH_2	H	Ph	**4g**, 94
8	CH_2CH_2	H	*p*-FC_6H_4	**4h**, 79
9	CH_2CH_2	H	*p*-$MeOC_6H_4$	**4j**, 48
10	CH_2CH_2	Me	H	**4m**, 61
11	CH_2	Me	H	**4n**, 80
12	CH_2CH_2	*i*Pr	H	**4o**, 60
13	CH_2	*i*Pr	H	**4p**, 84
14	CH_2CH_2	Ph	H	**4q**, 63
15	CH_2	Ph	H	**4r**, 67
16	CH_2CH_2	allyl	H	**4s**, 68
17	CH_2	*t*Bu	H	**4t**, 78
18	CH_2	*p*-$OMeC_6H_4$	H	**4u**, 65
19	CH_2	*p*-ClC_6H_4	H	**4v**, 86
20		H	H	**4w**, 19

[a] Isolated yield.

good yields (Table 3). In some cases, the volatility of the aldehyde reduced the isolated yield. However, if precautions were accordingly taken with the solvent evaporation process, good yield could be maintained. Surprisingly, allenol **6w**[27] furnished the corresponding aldehyde **4w** in low yield (19%; Table 3, entry 20). In most cases, allenals **4** could be stored at −20 °C for a few weeks. This set of aldehydes **4** constitutes a library with substantial molecular diversity, including chain length, substitution pattern of the allene function, and heteroatom functionalization that will allow for the synthesis of novel heterocycles.

Asymmetric Pictet–Spengler Reactions

The asymmetric Pictet–Spengler reaction was used as the key step for the asymmetric construction of **1**. Tryptamines previously reported in such process were protected either by sulfenyl,[14b] benzyl,[14c] or 2-naphthylmethyl (NAP)[14d] groups. The key point for our strategy was accordingly the compatibility of the *N*-allyl protecting group[28] and the 1,*n*-allenals **4** with phosphoric acid-catalyzed asymmetric Pictet–Spengler reactions. In our initial studies,[18] we demonstrated the ability of the allyl group to act as a protecting group for tryptamine in Pictet–Spengler reactions and the compatibility of the allene function with the reaction conditions. In particular, we found that the spinol-derived[14d] chiral phosphoric acid **15** was the best catalyst for the asymmetric Pictet–Spengler reaction of *N*-allyl tryptamines **3** with allenals **4**. Asymmetric catalytic Pictet–Spengler reactions were accordingly performed by reaction of *N*-allyl tryptamines **3a–c** with the extended set of aldehydes **4** (3 equiv)[29] in the presence of the Spinol-derived catalyst **10** (2 mol%; Scheme 2). The corresponding tetrahydro-β-carbolines **2a–s** were obtained in essentially good yields and excellent enantioselectivities (87–97% *ee*).[30] Overall, we found that the length and the functionalization of the side chain have little influence on the enantiomeric excesses. In addition, neither the substituent R^3 present on the tryptamine moiety nor

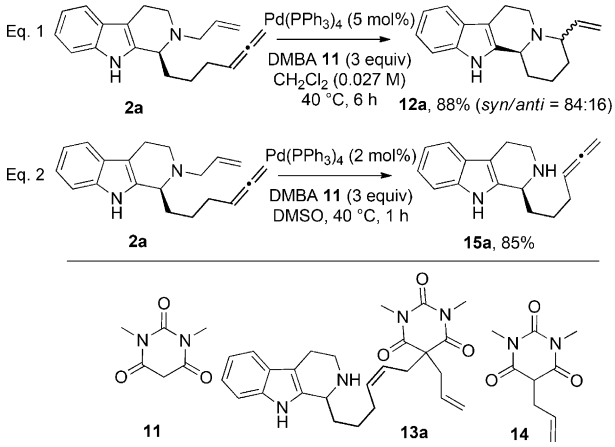


Scheme 2. Scope of the asymmetric Pictet–Spengler reaction.

the R^1 group of the allene affected the enantioselectivity or the yield of these reactions significantly. Notably, previously unknown compounds bearing various R^1 groups were obtained in good yields and enantiomeric excesses. The only exception was compound **2s**, for which the *p*-ClPh group lowered both the yield and the *ee* to 54 and 87%, respectively. In addition, compound **2r**, bearing an electron-rich aryl group was not obtained, with the reaction leading to degradation products. Similarly, aldehyde **4w** did not afford compound **2t**.

Pd^0-Catalyzed Cyclizations

After establishing the synthesis of enantioenriched tetrahydro-β-carbolines **2**, their palladium-catalyzed cyclizations were then investigated. In our initial studies,[18] we found that a catalytic system composed of 5 mol% tetrakis(triphenylphosphine) palladium and dimethylbarbituric acid **11** as the allyl scavenger[31] furnished, at a concentration of 0.027 M, compound **12a** in 88% yield as a 84:16 separable mixture of *cis* and *trans* diastereoisomers (Scheme 3, Eq. 1). Additional extensive studies

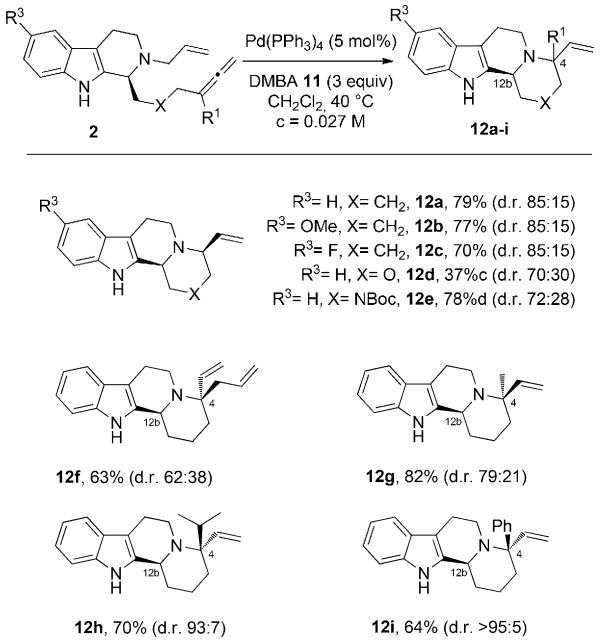


Scheme 3. Selective formation of tetracycle **12a** or amine **15a**.

showed that, depending on the reaction conditions, the formation of compound **12a** was accompanied by substantial amounts of olefin **13a**, which resulted from intermolecular addition of monoallyl-DMBA **14** to the allene function (see proposed mechanism). In addition, we found that the intermediate deprotected amine **15a** could be obtained cleanly and selectively by reducing the amount of catalyst and by performing the reaction in dimethyl sulfoxide (DMSO) within one hour (Scheme 3, Eq. 2). The method provides efficient access to this amine that will be further used for mechanistic studies.

6-*exo*-Cyclizations

The enantioenriched tetrahydro-β-carbolines **2** were then submitted to the conditions previously established for the palladium-catalyzed tandem allyl deprotection/cyclization process. Compounds presenting a 1,6-relationship between the amine and the allene function gave the corresponding six-membered



Scheme 4. 6-*exo*-Cyclizations to indoloquinolizidines **12**.

rings **12a–i** through 6-*exo*-cyclization on the allene (Scheme 4). Diastereoisomeric pairs of compounds were separated on silica gel[32] and characterized independently by NMR techniques. Indolo[2,3-*a*]quinolizidines substituted with a methoxy or fluoride group, led to heterocycles **12b** and **12c** in good yields and diastereoselectivities, supporting the conclusion that the nature of the substituents on the indole has little influence. Substrates displaying a heteroatom in the chain led to the corresponding vinyl-morpholine **12d** and piperazine **12e** in 37 and 78% yields, respectively.

We then focused on the cyclization of *gem*-disubstituted allenes, potentially leading to piperidines with stereocontrolled quaternary centers in the 4-position (Scheme 4). The reaction of tetrahydro-β-carbolines **2j–m** furnished the corresponding cyclized compound **12f–i** through a 6-*exo*-cyclization pathway. We noticed that the diastereoselectivity ratio increased with the steric bulk of the R^1 group. Whereas the less bulky allyl group led to a moderate diastereoisomeric ratio (d.r. = 62:38), the diastereoselectivity increased to 79:21 when R^1 = Me and to 93:7 when R^1 = *i*Pr. The use of a substrate with a phenyl group substituent led to **12i** with complete diastereocontrol in 64% yield. Notably, in all cases, the main diastereoisomer presents a *cis* relationship between H12b and the smaller substituent of C4.

The stereochemistry of the *cis*/*trans* diastereoisomers was assigned based on 2D NMR techniques (Figure 2). Compound **12a** presents all relevant NOE correlations between H-4, H-6b, H-12b, and H-2 characteristic for 1,3-diaxial interactions and a NOE correlation between H-6a and the vinylic proton. Similarly, the major diastereoisomer of **12h** (R^1 = *i*Pr) shows correlations between H-12b, H-6b, and the vinylic proton, and a correlation between H-6a and the *i*Pr group.

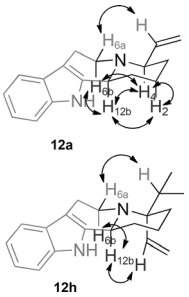
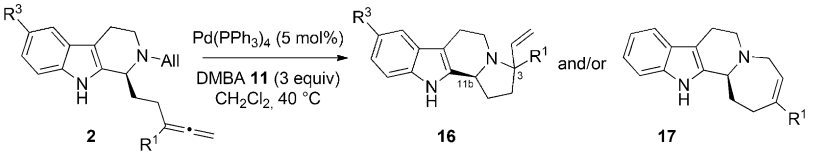


Figure 2. Relevant NOESY correlations for compounds **12a** and **12h**.

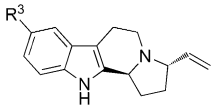
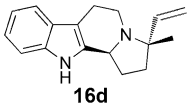
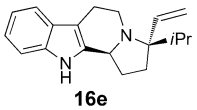
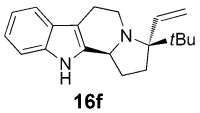
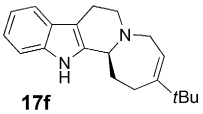
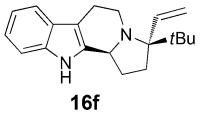
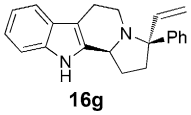
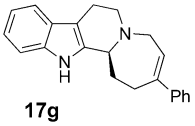
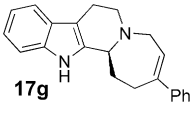
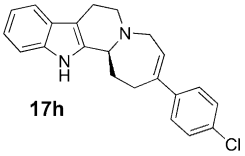
5-*exo*- and 7-*endo*-Cyclizations

The series of compounds **2d**–**f** and **2n**–**s**, possessing a 1,5-relationship between the amine and the allene, were successfully submitted to cyclizations. Interestingly, the reaction proceeded through either a 5-*exo*- or 7-*endo*-cyclization pathway, depending on the substitution pattern of the allene and on the concentration of the reaction mixture (Table 4). 5-*exo*-Cyclizations furnished indolizino[8,7-*b*]indoles **16**, whereas 7-*endo*-cyclizations led to azepino[1′,2′:1,2]pyrido[3,4-*b*]indoles **17**, both scaffolds being encountered in natural products with biological activities.[33] Diastereoisomeric mixtures of **16** were separated on silica gel and the corresponding *cis*/*trans* derivatives were characterized by 2D NMR techniques. Allenes **2d**–**f** underwent selective 5-*exo*-cyclizations to indolo[2,3-*a*]pyrrolizidines **16a**–**c** in good yields with diastereoisomeric ratios of approximately 75:25 (Table 4, entry 1). In contrast, with the indolo[2,3-*a*]quinolizidines **12** series, the major diastereoisomer obtained presents a *trans*-relationship between H-3 and H-11b. In these cases, we found that dilution of the reaction mixture to 0.01 M was beneficial to both the yield and the diastereoselectivity. The introduction of an R^1 substituent on the allene afforded five-membered rings **16d**–**e** with quaternary centers in moderate to excellent diastereoselectivities in the case of R^1 = Me and R^1 = *i*Pr, respectively (Table 4, entries 2–3). The increase in the steric bulk of the R^1 group from *i*Pr to *t*Bu promoted a different cyclization pattern. With a *t*Bu group, we obtained a 1:1 mixture of compounds **16f** and **17f** in 61% yield, resulting from 5-*exo*-and 7-*endo*-cyclization pathways, respectively (Table 4, entry 4). When the concentration was increased (0.1 M), a mixture was again obtained (Table 4, entry 5), whereas high dilution (0.01 M) afforded the indolizidine **16f** chemoselectively in 62% yield, as a sole diastereoisomer (Table 4, entry 6). Similarly, by using phenyl-substituted allene **2q**, the cyclization afforded a 25:75 mixture of **16g** and **17g**, respectively, when the reaction was performed at 0.01 M (Table 4, entry 7), whereas concentrated conditions (0.1 M) afforded the 7-*endo*-cyclization product **17g** regioselectively in 76% yield (Table 4, entry 8). The latter results indicate that the cyclization pathway is not only governed by the steric bulk of

Table 4. Regioselective 5-*exo*- or 7-*endo*-cyclizations to heterocycles **16** or **17**.



2 16 17

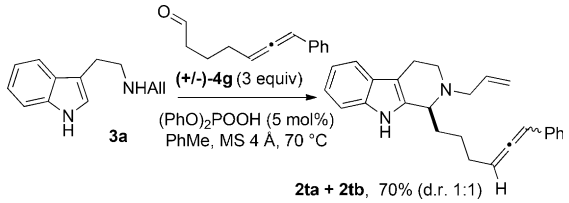
Entry	2	c [M]	Product 16[a]	or 17	Ratio 16/17[b]	d.r. (16)[b]	Yield [%][c]
1	**2d** (R^3 = H), **2e** (R^3 = OMe), **2f** (R^3 = F)	0.01	 **16a-c**		100:0	75:25 79:21 73:27	80 67 79
2	**2n**	0.027	 **16d**		100:0	55:45	67
3	**2o**	0.027	 **16e**		100:0	9:91	64
4	**2p**	0.027	 **16f**	 **17f**	50:50	>95:5	61
5	**2p**	0.1	 **16f**		68:32	>95:5	81
6	**2p**	0.01			100:0	>95:5	62
7	**2q**	0.01	 **16g**	 **17g**	25:75	>77:23	87
8	**2q**	0.1		 **17g**	0:100	–	76
9	**2s**	0.1		 **17h**	0:100	–	63

[a] The major diastereomer is shown. [b] Ratio measured by ^{1}H NMR spectroscopic analysis. [c] Yield is given for pure, isolated compounds **16** or **17**, or for both when mixtures were obtained.

the R^2 substituent but also by its electronic nature. Replacement of the phenyl substituent by a 4-chlorophenyl group afforded the 7-*endo*-cyclized product **17h** in 63% yield with full regioselectivity (Table 4, entry 9).

Case of 1,3-Disubstituted Allenes

The Pictet–Spengler reactions reported above and subsequent cyclizations to polycyclic compounds were accomplished at first with monosubstituted and *gem*-disubstituted allenes. We then investigated the case of 1,3-disubstituted allenes **4g–h**. The reaction of tryptamine **3a** with aldehyde (+/−)-**4g** in the presence of diphenyl phosphate furnished the corresponding tetrahydro-β-carboline **2t** in 70% yield, as a 1:1 mixture of two diastereoisomers **2ta** and **2tb** (Scheme 5). Purification on silica



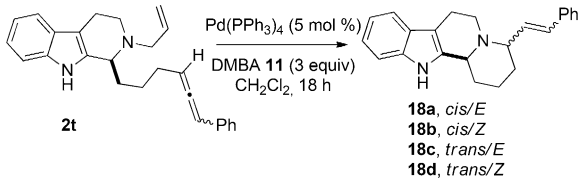
Scheme 5. Pictet–Spengler reaction with racemic aldehyde **4g**.

gel afforded both diastereoisomers separately, which were characterized independently.

We then turned our attention to the cyclization of **2t** under the conditions established previously. The palladium-catalyzed deprotection/cyclization was performed on either the mixture of diastereoisomers **2ta** and **2tb**, or on each diastereoisomer, independently. All the cyclizations furnished the desired piperidine **18**; the case is, however, complicated by the presence of three out of four possible diastereoisomers **18a–d**, due to the geometry of the newly-formed double-bond. Indeed, when the reaction was performed with a 1:1 mixture of **2ta**/**2tb**, a separable mixture of three diastereoisomers **18a–c** was obtained in 68% global yield (Table 5, entry 1) after a few hours at room temperature. When the reaction was performed independently with both diastereoisomers **2ta** and **2tb**, the ratio changed dramatically. Whereas the diastereoisomer **2ta** furnished **18b** as the main product (Table 5, entry 2), the cyclization of **2tb** led to **18a** as the main compound, albeit with a lower global yield (Table 5, entry 3). It should, however, be noted that despite the complexity of the reaction mixtures, the global *cis*/*trans* ratio ([**18a**+**18b**]/**18c** ratio) remained very similar in all cases (ca. 73:27), irrespective of the geometry of the double bond. In addition, the fourth possible diastereoisomer **18d** was never obtained. It is consequently clear that the initial geometry of the allene affects the stereochemical outcome of the reaction, although it was previously reported that the chiral information of the allene is lost in such a palladium-catalyzed process.[34]

The three diastereoisomers **18a–c** were fully characterized by 1D and 2D NMR methods to determine the *cis*/*trans* relationship between both stereogenic centers and the *E*/*Z* geometry of the double bond. Measured coupling constants between H-1 and H-2 were found to be characteristic for the *Z* geometry ($J_{H1,H2}$ = 11.9 Hz) and *E* geometry ($J_{H1,H2}$ = 15.9 Hz) of the double bond, allowing for the determination of the double bond configurations in each product.

Table 5. Optimization for the one-pot deallylation/cyclization

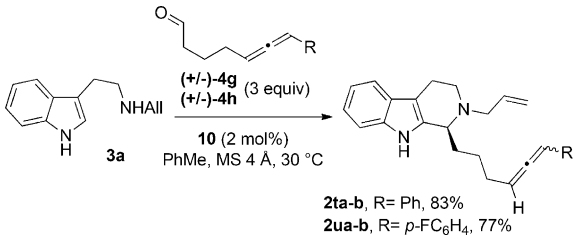


Entry	2	T [°C]	18a–d ratio	Global *cis*/*trans* ratio	Global yield [%][d]
1	**2ta–b**[a]	RT	33:40:27:0[b]	73:27	68
2	**2ta**	RT	10:62:28:0[b]	72:28	69
3	**2tb**	RT	66:7:27:0[c]	73:27	50

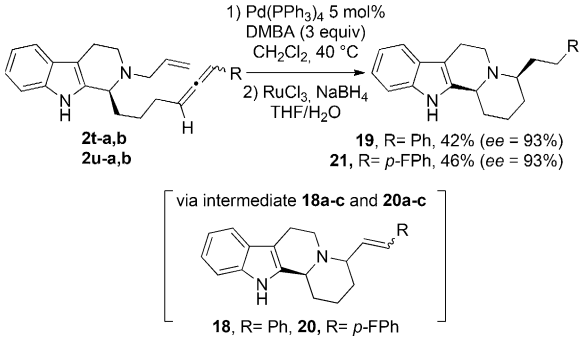
[a] 1:1 mixture. [b] Ratios were measured on the crude mixture by ^{1}H NMR spectroscopic analysis. [c] Ratio measured on purified products. [d] Isolated yield.

Asymmetric Pictet–Spengler reactions were then performed between tryptamine **3a** and aldehydes (+/−)-**4g** and (+/−)-**4h**, in the presence of the chiral catalyst **10**, affording the corresponding compounds in good yields (Scheme 6) as mixtures of diastereoisomers. The enantiomeric excess determinations were measured in a subsequent step.

The enantioenriched compounds **2ta–b** and **2ua–b** were then submitted to palladium-catalyzed cyclization, furnishing mixtures of diastereoisomers **18a–c** and **20a–c** (Scheme 7, step 1). In an effort to avoid the troublesome purification of the diastereoisomeric mixtures, it was envisaged to submit the crude cyclization mixtures to a reduction step of the double bonds to simplify the purification of the compounds. Accord-

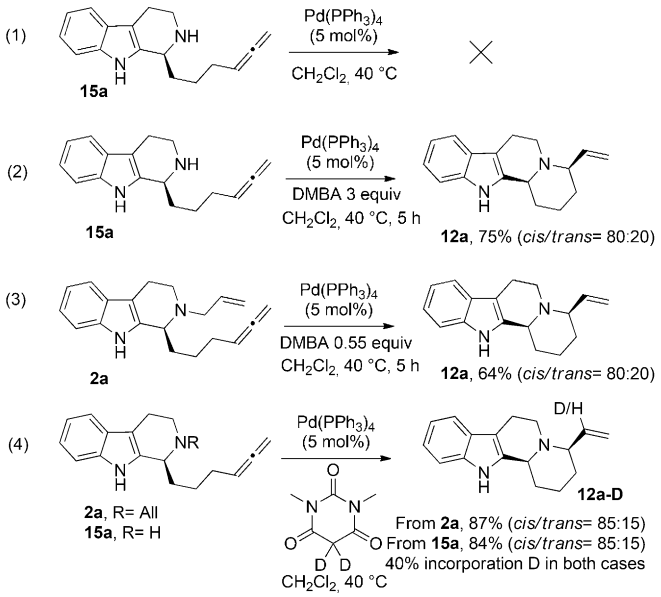


Scheme 6. Enantioselective synthesis of tetrahydro-β-carbolines **2t–u**.



Scheme 7. Cyclization/reduction strategy to compounds **19** and **21**.

ingly, the crude mixtures resulting from the palladium-catalyzed reactions were submitted to $NaBH_4$, in the presence of a catalytic amount of $RuCl_3$ (Scheme 7, step 2).[35] We found that a short purification to remove the DMBA derivatives was necessary prior to the reduction step. The reductions were then performed only on the *cis* diastereoisomers **18a**,**b** and **20a**,**b**.[36] This approach led rapidly to **19** and **21** in 42 and 46% yields, respectively (two steps). The enantiomeric excesses of **19** and **21** were then found to be 93%, demonstrating the compatibility of 1,3-disubstituted allene functions with asymmetric Pictet–Spengler conditions.

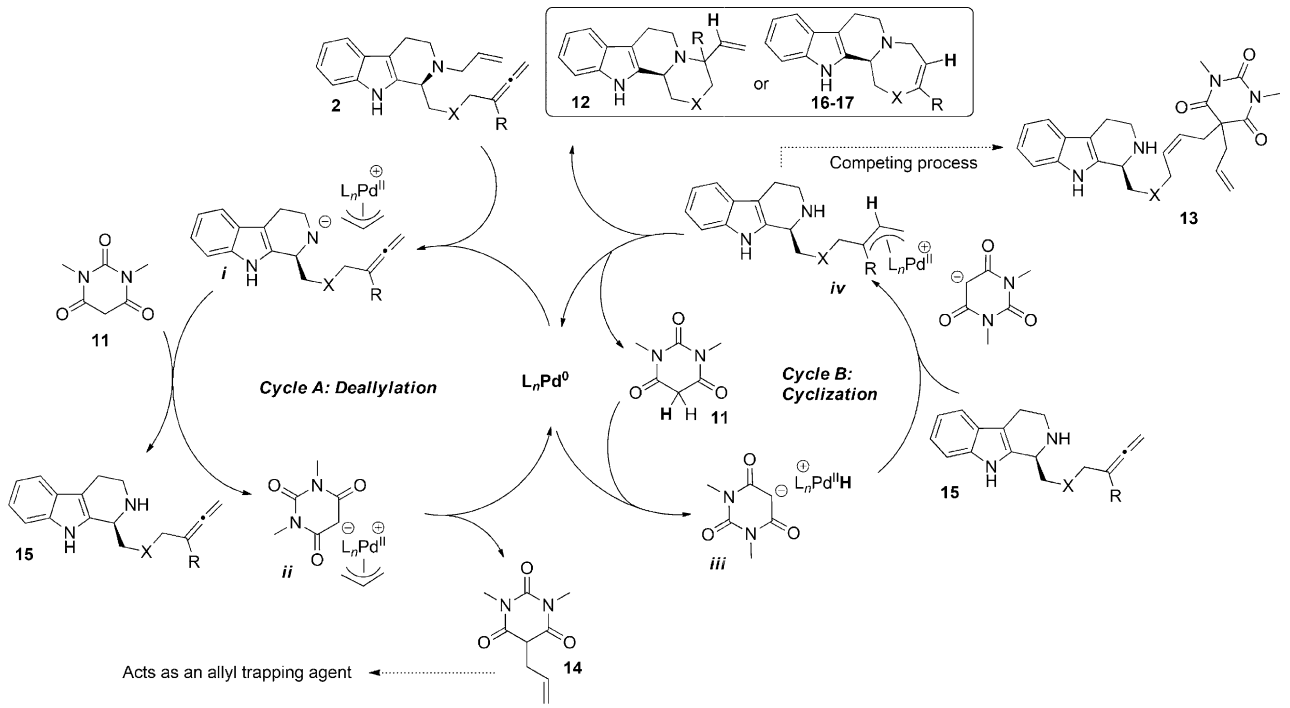


Scheme 8. Mechanistic investigations.

Mechanistic Studies

Experiments were performed to gather more information on the mechanism and to better understand the role of each component in the reaction (Scheme 8). We performed in particular a set of experiments to understand and demonstrate the pivotal role of DMBA in the reaction. The deprotected amine **15a** was reacted with a catalytic amount of $Pd(PPh_3)_4$, leading to no reaction (Scheme 8, Eq. 1). In contrast, when the same reaction was performed in the presence of three equivalents of DMBA **11**, the product **12a** was obtained in 75% yield in a 83:17 d.r., which is similar to that obtained from allyl-protected compound **2a** (Scheme 8, Eq. 2). These results demonstrate clearly the involvement of DMBA **11** in the cyclization step. DMBA also plays a critical role in scavenging the allyl cation prior to cyclization. We have observed that diallyl-DMBA is the only DMBA-derivative formed during the reaction, showing that 0.5 equivalent is enough to bring deallylation to completion. Indeed, the tandem deprotection/cyclization process performed with 0.55 equivalent furnished the desired compound **12a** in 64% yield and in good diastereoselectivity (Scheme 8, Eq. 3). Interestingly, when deuterated DMBA was used in the presence of palladium catalyst from **2a** or **15a**, the cyclized products **12a-D** were obtained in excellent yields, with 40% incorporation of deuterium on the vinyl proton (Scheme 8, Eq. 4). This rate of incorporation is lowered by scrambling phenomena between exchangeable protons of **2a** and **15a** and the reactant.[37] All these experimental results account for the critical role of DMBA for both the deallylation, as trapping agent, and the cyclization.

The tandem deprotection/cyclization process may consequently be the result of two combined catalytic cycles A and B



Scheme 9. Postulated mechanism for the tandem deprotection/cyclization process.

in which DMBA **11** is involved. Cycle A is a classical Pd-catalyzed allyl group removal,[38] and cycle B is the Pd-catalyzed addition of the intermediate deprotected amine to the allene (Scheme 9).[39] The addition of pronucleophiles to allenes,[34,40] including amines,[34,40c–e,g] catalyzed by Pd^0 is a known atom-economic[41] strategy for allylic functionalization from allenes. It has been shown, in particular by Trost,[40l] to proceed via a hydridopalladium species, the formation of which has been shown to be facilitated by the adjunction of an acid cocatalyst.[42]

On the basis of our results and on reported precedents, the mechanism shown in Scheme 9 can be suggested. Starting material **2** enters in the first catalytic cycle and reacts with Pd^0 to generate a π-allyl species **i**, which, in turn, is trapped by DMBA **11**, thus liberating the intermediate tetrahydro-β-carboline **15** and the monoallyl DMBA **14**.[43] The reaction of Pd^0 with the proton donor DMBA **11** generates Pd^{II}-H **iii**,[40h] which adds to the allene through hydropalladation, resulting in the formation of π-allyl complex **iv**. Subsequent intramolecular allylic substitution by the nucleophilic amine through either 6-*exo*- or 7-*endo*-attack leads to the products **12**, **16**, or **17**, depending on the chain length. Intramolecular trapping of the π-allyl complex also ensures regeneration of DMBA **11** and Pd^0.

Competing intermolecular allylic substitution of monoallyl-DMBA **14** on intermediate **iv** explains the formation of compound **13**. It becomes clear that this intermolecular process is strongly favored under concentrated conditions, whereas dilute conditions favor the intramolecular process. In addition, when the cyclization is not favored, the π-allyl complex **iv** can only evolve toward the DMBA addition product **13**.

The success of the reaction is consequently the result of a very fine balance between inter- and intramolecular reactions and *exo*- or *endo*-cyclization pathways.

Conclusion

Numerous 1,*n*-allenaldehydes **4**, possessing different substitution patterns, were successfully engaged in Brønsted acid-catalyzed Pictet–Spengler reactions with *N*-allyltryptamines, leading to functionalized tetrahydro-β-carbolines **2**, bearing pendent allene functions, in good yields and enantiomeric excess. A palladium-catalyzed strategy was used to trigger both the *N*-allyl deprotection and the cyclization of the intermediate amine on the allene function via a transient π-allyl-Pd intermediate. Depending on the chain length and substitution pattern of the allene function, regioselective cyclizations occurred through 5-*exo*-, 6-*exo*-, or 7-*endo*-mechanisms, affording various tetracyclic compounds. The mechanism of the tandem reaction consists of two distinct catalytic cycles involving Pd^0 through "self-relay catalysis".[44] This tandem process saves the deprotection step and allows an atom-economical formation of the π-allyl. In addition, the dimethyl barbituric acid used as the allyl scavenger is also pivotal in the generation of the Pd^{II}-H intermediate. Notably, the method has been applied to unprotected indole derivatives. Taken together, this tandem process can be considered as a step- and atom-economical process for the rapid and selective elaboration of complex, enantioenriched, polycyclic indolic compounds.

Experimental Section

Detailed descriptions of experimental procedures, spectral data and ^1H and ^{13}C NMR spectra of all new compounds are given in the Supporting Information.

General procedure for the Swern oxidation: Oxalyl chloride (1.5 equiv) was dissolved in CH_2Cl_2 in a flask under an argon atmosphere. The reaction mixture was then cooled at −78 °C and DMSO (3 equiv) was added dropwise. Stirring was continued at −78 °C for 30 min, followed by dropwise addition of a solution of alcohol **6** (1 equiv) dissolved in CH_2Cl_2. The reaction mixture was further stirred for 1 h and Et_3N (6 equiv) was added. The reaction mixture was then allowed to warm to RT. Water was added, the organic layer was separated, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under vacuum. The crude mixture was then purified by flash chromatography to give the desired product **4**.

Typical procedure for 5-phenylhepta-5,6-dienal (4q): Prepared according to the general procedure from **6q** (550 mg, 2.921 mmol), oxalyl chloride (0.38 mL, 4.382 mmol), DMSO (0.62 mL, 8.763 mmol) and Et_3N (2.44 mL, 17.256 mmol) in CH_2Cl_2 (17 mL). Compound **4q** was obtained after column chromatography on silica gel (MTBE/petroleum ether, 5:95). Yield: 340 mg (1.825 mmol, 63%); colorless oil; R_f = 0.27 (MTBE/petroleum ether, 5:95); IR (neat): $\tilde{\nu}$ = 2951, 2721, 1940, 1723, 1494, 1452, 855, 764, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 9.77 (t, J = 1.6 Hz, 1H; H-1), 7.39–7.35 (m, 2H; 2×ArH), 7.33–7.28 (m, 2H; 2×ArH), 7.22–7.16 (m, 1H; ArH), 5.08 (t, J = 3.3 Hz, 2H; 2×H-7), 2.52 (td, J = 7.3, 1.7 Hz, 2H; 2×H-8), 2.49–2.43 (m, 2H; 2×H-4), 1.90 ppm (q, J = 7.3 Hz, 2H; 2×H-3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.7 (C_q, C6), 202.5 (CH, C1), 136.1 (C_q, C_{Ar}), 128.7 (CH, 2×C_{Ar}), 127.0 (CH, C_{Ar}), 126.1 (CH, 2×C_{Ar}), 104.4 (C_q, C5), 78.9 (CH_2, C7), 43.6 (CH_2, C2), 29.0 (CH_2, C4), 20.5 ppm (CH_2, C3).

General procedure for the enantioselective Pictet–Spengler reaction: A mixture of N_β-α-allyl tryptamine **3** (1 equiv), catalyst **10** (0.02 equiv), and 4 Å molecular sieves (0.23 g for 0.35 mmol of **3**, powdered) in toluene (1.5 mL for 0.1 mmol of **3**) was stirred for 5 min at RT under an argon atmosphere. Aldehyde **4** (3 equiv) was added and the mixture was stirred at 30 °C for 16 h. Upon completion of the reaction (TLC monitoring), the reaction mixture was filtered over silica. The filtrate was concentrated under vacuum and the residue was purified by flash chromatography to give the desired product **2**.

Typical procedure for (*S*)-2-allyl-1-(4-phenylhexa-4,5-dien-1-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (2l): Prepared according to the general procedure from **3a** (70 mg, 0.350 mmol), **4q** (196 mg, 1.050 mmol), **10** (5.2 mg, 0.007 mmol), and 4 Å molecular sieves (230 mg) in toluene (5.2 mL). Purification on silica gel (EtOAc/petroleum ether, 5:95 to 10:90) afforded **2l**. Yield: 96 mg (0.261 mmol, 74%); yellow oil; R_f = 0.15 (EtOAc/petroleum ether, 5:95). $[\alpha]_D^{26}$ = +0.5 (*c* 1.00, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3413, 3056, 2931, 1940, 1493, 1451, 1300, 1155, 1171, 996, 919, 851, 763, 740, 695 cm^{-1}; *ee* = 95% {Chiralpak AD-H column; heptanes/IPA, 95:5 + 0.1% Et_3N; 1 mL min^{-1}; λ = 277 nm; t_R = 6.49 (major), 8.24 min (minor)}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.51 (s, 1H; H-9), 7.46 (dd, J = 7.1, 1.5 Hz, 1H; ArH), 7.39 (dd, J = 7.3, 1.6 Hz, 2H; 2×ArH), 7.33–7.26 (m, 3H; 3×ArH), 7.22–7.16 (m, 1H; ArH), 7.15–7.04 (m, 2H; 2×ArH), 5.91 (dtt, J = 16.9, 10.3, 6.5 Hz, 1H; H-17), 5.15–5.04 (m, 4H;

2×H-18 and 2×H-15), 3.68 (t, J=5.8 Hz, 1H; H-1), 3.26–3.17 (m, 3H; 2×H-16 and H-3a), 2.93 (ddd, J=13.4, 5.2, 3.4 Hz, 1H; H-3b), 2.86–2.75 (m, 1H; H-4a), 2.59–2.44 (m, 3H; H-4b and 2×H-12), 1.88–1.70 ppm (m, 4H; 2×H-10 and 2×H-11); ^{13}C NMR (75 MHz, $CDCl_3$): δ=208.9 (C_q, C14), 137.0 (CH, C17), 136.6 (C_q, C_{Ar}), 136.0 (C_q, C_{Ar}), 135.5 (C_q, C_{Ar}), 128.7 (CH, 2×C_{Ar}), 127.5 (C_q, C_{Ar}), 126.9 (CH, C_{Ar}), 126.3 (CH, 2×C_{Ar}), 121.6 (CH, C_{Ar}), 119.5 (CH, C_{Ar}), 118.2 (CH, C_{Ar}), 117.4 (CH_2, C18), 110.8 (CH, C_{Ar}), 108.2 (C_q, C_{Ar}), 105.0 (C_q, C13), 78.3 (CH_2, C15), 56.5 (CH_2, C16), 56.2 (CH, C1), 45.3 (CH_2, C3), 34.0 (CH_2, C10), 29.8 (CH_2, C12), 24.8 (CH_2, C11), 18.2 ppm (CH_2, C4); HRMS (ESI): m/z calcd for $C_{26}H_{29}N_2$ 369.2335 $[M+H]^+$; found 369.2331.

General procedure for the tandem Pd^0-catalyzed deprotection/cyclization: Tetrahydro-β-carboline **2** (1 equiv), $Pd(PPh_3)_4$ (0.05 equiv), and 1,3-dimethylbarbituric acid **11** (3 equiv) were introduced in a reaction flask that was purged with argon. CH_2Cl_2 was then added and the mixture was stirred at 40 °C or RT for 6 h. Upon completion of the reaction, the mixture was cooled to RT and a saturated aqueous solution of $NaHCO_3$ was added. The organic layer was separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under vacuum. The crude mixture was then purified by flash chromatography to give the desired products **12**, **16**, **17**, or **18**.

Typical procedure for (4*S*,12b*S*)-4-phenyl-4-vinyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (12i): Prepared according to the general procedure using **2l** (75 mg, 0.203 mmol), $Pd(PPh_3)_4$ (11.7 mg, 0.010 mmol), and DMBA **11** (95 mg, 0.609 mmol) in CH_2Cl_2 (7.5 mL). Purification on silica gel (EtOAc/petroleum ether, 2.5:97.5) afforded **12i**. Yield: 44 mg (0.134 mmol, 66%); yellow oil; R_f=0.27 (EtOAc/petroleum ether, 2.5:97.5); $[\alpha]_D^{25}$=−48.2 (*c* 1.00, $CHCl_3$); IR (neat): $\tilde{\nu}$=3421, 2057, 2928, 2845, 1597, 1446, 1379, 1301, 1215, 1109, 1032, 1005, 923, 739, 703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.69 (s, 1H; ArH), 7.65 (s, 1H; H-12), 7.45 (d, J=7.6 Hz, 1H; ArH), 7.33–7.28 (m, 2H; 2× ArH), 7.24–7.20 (m, 1H; ArH), 7.11 (t, J=7.6 Hz, 1H; ArH), 7.06 (t, J=7.7 Hz, 1H; ArH), 6.14 (dd, J=18.0, 11.4 Hz, 1H; H-13), 5.68 (dd, J=11.2, 1.3 Hz, 1H; H-14a), 5.36 (dd, J=18.0, 1.2 Hz, 1H; H-14b), 3.95 (d, J=9.8 Hz, 1H; H-12b), 2.97–2.92 (m, 1H; H-6a), 2.82–2.75 (m, 1H; H-7a), 2.57–2.50 (m, 2H; H-6b and H-7b), 2.13–2.06 (m, 2H; H-3a and H-1a), 1.91–1.84 (m, 1H; H-2a), 1.77–1.65 ppm (m, 3H; H-1b, H-2b and H-3b); ^{13}C NMR (125 MHz, $CDCl_3$): δ=148.3 (C_q, C_{Ar}), 136.9 (C_q, C_{Ar}), 136.3 (C_q, C_{Ar}), 135.7 (CH, C13), 128.4 (CH, C_{Ar}), 127.7 (C_q, C_{Ar}), 126.9 (CH, 2×C_{Ar}), 126.8 (CH, 2×C_{Ar}), 121.4 (CH, C_{Ar}), 119.6 (CH, C_{Ar}), 119.2 (CH_2, C14), 118.3 (CH, C_{Ar}), 110.8 (CH, C_{Ar}), 109.2 (C_q, C_{Ar}), 66.8 (C_q, C4), 54.7 (CH, C12b), 45.9 (CH_2, C6), 38.5 (CH_2, C1), 31.9 (CH_2, C3), 22.5 (CH_2, C7), 21.4 ppm (CH_2, C2); HRMS (ESI): m/z calcd for $C_{23}H_{25}N_2$ 329.2018 $[M+H]^+$; found 329.2012.

(*S*)-3-Phenyl-2,5,7,8,13,13b-hexahydro-1*H*-azepino[1′,2′:1,2]pyrido[3,4-*b*]indole (17g): Prepared according to the general procedure using **2q** (37 mg, 0.104 mmol), $Pd(PPh_3)_4$ (6 mg, 0.055 mmol), and DMBA **11** (49 mg, 0.312 mmol) in CH_2Cl_2 (1.0 mL). Purification on silica gel (EtOAc/heptane, 50:50) afforded **17g**. Yield: 25 mg (0.079 mmol, 76%); yellow powder; R_f=0.26 (EtOAc/heptane, 50:50); $[\alpha]_D^{25}$=−92.7 (*c* 1.00, $CHCl_3$); IR (neat): $\tilde{\nu}$=2922, 2849, 1483, 1448, 1340, 1237, 1129, 1076, 1038, 909, 815, 742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.73 (s, 1H; H-13), 7.48 (d, J=7.5 Hz, 1H; ArH), 7.35–7.21 (m, 6H; 6×ArH), 7.16–7.06 (m, 2H; 2×ArH), 6.04 (td, J=5.7, 1.1 Hz, 1H; H-4), 4.22 (dd, J=10.4, 4.0 Hz, 1H; H-13b), 3.65 (dd, J=15.6, 5.1 Hz, 1H; H-5a), 3.52 (dd, J=16.0, 6.0 Hz, 1H; H-5b), 3.27–3.19 (m, 1H; H-7a), 3.04–2.88 (m, 3H; H-7b, H-2a and H-8a), 2.85–2.68 (m, 2H; H-2b and H-8b), 2.27–2.19 (m, 1H; H-1a), 2.06–1.94 ppm (m, 1H; H-1b); ^{13}C NMR (75 MHz, $CDCl_3$): δ=144.0 (C_q, C3), 136.3 (C_q, C_{Ar}), 135.9 (C_q, C_{Ar}), 133.8 (C_q, C_{Ar}), 128.6 (CH, 2×C_{Ar}), 127.2 (CH, C4), 127.2 (C_q, C_{Ar}), 126.2 (CH, 2×C_{Ar}), 121.9 (CH, C_{Ar}), 119.8 (CH, C_{Ar}), 118.6 (CH, C_{Ar}), 111.1 (CH, C_{Ar}), 108.8 (C_q, C_{Ar}), 61.7 (CH, C13b), 52.9 (CH_2, C5), 51.0 (CH_2, C7), 31.2 (CH_2, C1), 30.5 (CH_2, C2), 21.0 ppm (CH_2, C8); HRMS (ESI): m/z calcd for $C_{22}H_{23}N_2$ 315.1861 $[M+H]^+$; found 315.1875.

Synthesis of (4*R*,12b*S*)-4-phenethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (19): Tetrahydro-β-carboline **2t** (120 mg, 0.326 mmol, two diastereoisomers), $Pd(PPh_3)_4$ (18.7 mg, 0.016 mmol), and 1,3-dimethylbarbituric acid **11** (152 mg, 0.978 mmol) were introduced in a reaction flask that was purged with argon and dissolved in CH_2Cl_2 (12 mL). The reaction mixture was stirred at RT for 16 h. A saturated aqueous solution of $NaHCO_3$ was added, the organic layer was separated, and the aqueous phase was extracted twice with CH_2Cl_2. Combined organic layers were dried with $MgSO_4$, filtered, and concentrated under vacuum. The crude mixture was then purified by flash chromatography (EtOAc/heptane, 20:80 to 100% EtOAc) to give a mixture of **18a** and **18b** (65 mg, 0.199 mmol, 61%) and **18c** (11.7 mg, 0.036 mmol, 11%). The mixture of **18a** and **18b** (35 mg, 0.107 mmol) was introduced in a reaction flask that was purged with argon and dissolved in THF/H_2O (8 mL, 3:1). $RuCl_3{\cdot}3H_2O$ (3.6 mg, 0.006 mmol) and $NaBH_4$ (11.5 mg, 0.305 mmol) were then added and the mixture was stirred at 50 °C for 16 h. Upon completion of the reaction, the mixture was cooled to RT and a saturated aqueous solution of $NaHCO_3$ was added. The organic layer was separated, the aqueous phase was extracted twice with MTBE, and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated under vacuum. The crude mixture was then purified by flash chromatography (EtOAc/heptane, 20:80 to 40:60) to afford *cis*-**19**. Yield: 24 mg (0.073 mmol, 69%); orange oil; R_f=0.25 (heptane/EtOAc, 65:35); $[\alpha]_D^{25}$=−25.9 (*c* 1.00, $CHCl_3$); IR (neat): $\tilde{\nu}$=3409, 2928, 2854, 1574, 1509, 1465, 1301, 1259, 1216, 1158, 1059, 1036, 870, 820, 737, 663 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN): δ=8.90 (s, 1H; H-12), 7.41 (d, J=7.6 Hz, 1H; ArH), 7.33–7.25 (m, 5H; 5×ArH), 7.20–7.16 (m, 1H; ArH), 7.06 (t, J=7.3 Hz, 1H; ArH), 7.00 (t, J=7.6 Hz, 1H; ArH), 3.47 (dt, J=11.6, 3.7 Hz, 1H), 3.42 (d, J=9.5 Hz, 1H), 2.82–2.64 (m, 4H), 2.49–2.44 (m, 1H), 2.38–2.33 (m, 1H), 2.10–2.06 (m, 1H), 1.92–1.88 (m, 2H), 1.72–1.69 (m, 1H), 1.56–1.48 ppm (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=142.9 (C_q, C_{Ar}), 141.4 (C_q, C_{Ar}), 136.3 (C_q, C_{Ar}), 128.6 (CH, 2×C_{Ar}), 128.5 (CH, 2×C_{Ar}), 127.6 (C_q, C_{Ar}), 126.0 (CH, C_{Ar}), 121.5 (CH, C_{Ar}), 119.5 (CH, C_{Ar}), 118.3 (CH, C_{Ar}), 110.9 (CH, C_{Ar}), 108.4 (C_q, C_{Ar}), 61.4 (CH, C4), 60.3 (CH, C12b), 45.6 (CH_2, C6), 36.1 (CH_2, C13), 31.6 (CH_2, C14), 30.4 (CH_2, C1), 29.6 (CH_2, C3), 24.5 (CH_2, C2), 22.3 ppm (CH_2, C7); HRMS (ESI): m/z calcd for $C_{23}H_{27}N_2$ 331.2174 $[M+H]^+$; found 331.2199.

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Keywords: alkaloids · allenes · enantioselectivity · nitrogen heterocycles · palladium

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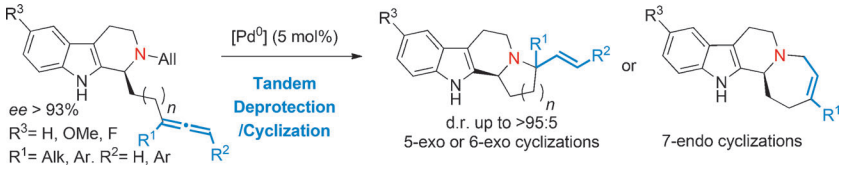

The right fold: Enantioenriched *N*-allyl tetrahydro-β-carbolines were prepared by chiral phosphoric acid-catalyzed Pictet–Spengler reactions. The compounds undergo Pd^0-catalyzed cyclizations through a tandem deprotection/cyclization process (see scheme). The regioselectivity of the attack is controlled by the chain length and by the substitution pattern of the allene function. Products resulting from 5-*exo*- or 6-*exo*-attack were obtained with diastereoisomeric ratios up to 95:5. Azepinopyrrido[3,4-*b*]indoles were obtained by 7-*endo*-cyclizations.

Alkaloids

*V. Gobé, X. Guinchard**

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Stereoselective Synthesis of Chiral Polycyclic Indolic Architectures through Pd^0-Catalyzed Tandem Deprotection/Cyclization of Tetrahydro-β-carbolines on Allenes