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Generation and reactions of 1-(2-indolyl)vinylcopper derivatives with pyridinium salts

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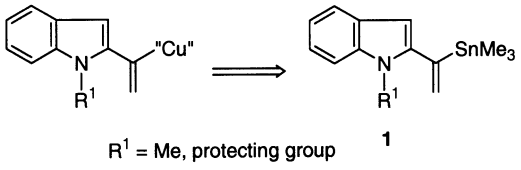
Abstract—1-(2-Indolyl)vinylstannane **1b** has been transmetallated into both the corresponding HO mixed cyanocuprate and the Cu-catalysed organomagnesium reagent, and the reactivity of these species towards *N*-alkyl-3-acylpyridinium salts **8** and **17** has been tested.

1. Introduction

Vinylstannanes[1] have become valuable reagents for the formation of C–C bonds. Although the main synthetic interest of vinylstannanes lies in their utility in palladium catalysed coupling (Stille) reactions,[2] they are also widely used as precursors of vinyllithiums.[1,3] Moreover, vinylstannanes have been directly converted into vinylcopper species either by ligand exchange with higher order (HO) cyanocuprates[4] or by transmetallation with copper(I) salts.[5]

In connection with our ongoing work in the synthesis of indole alkaloids, we considered the possibility that a variety of 2-vinylindole compounds could be prepared from vinylstannanes **1** through reactions of the corresponding 1-(2-indolyl)vinylcopper derivatives with appropriate acceptors (Scheme 1). Taking into account that the 2-vinylindole moiety is present in several indole alkaloids, either attached at the 4-position (uleine, apparicine)[6] or at the 2-position (ngouniensine)[6b] of the piperidine ring, the use of pyridinium salts as electrophilic partners in the above reactions particularly attracted our interest. In this context, we have recently reported that the addition of several organocopper reagents to 3-acyl-*N*-alkylpyridinium salts provides a flexible route to diversely substituted 1,2- and 1,4-dihydropyridines.[7,8] This paper deals with our results in the generation of 1-(2-indolyl)vinylcopper derivatives from vinylstannanes **1** and their participation in addition reactions to *N*-alkylpyridinium salts. To our knowledge, there are no precedents for the generation and use of 1-(indolyl)vinylcopper reagents in synthesis.



Scheme 1.

2. Results and discussion

Among the different procedures reported in the literature[1] for the preparation of vinylstannanes, we selected the one based on the Shapiro reaction[9] of 2,4,6-(triisopropyl)-phenylsulfonylhydrazones (trisylhydrazones) followed by quenching of the intermediate vinyl anions with Me_3SnCl.[10] Thus, the easily available 2-acetylindoles **2a–c** were converted into the corresponding trisylhydrazones **3a–c** in good yields (80–95%) by reaction with trisylhydrazide in CH_3CN (Scheme 2). Satisfactorily, *N*-methyl and *N*-unsubstituted vinylstannanes **1b** and **1c** could be easily prepared in 65 and 77% yield, respectively, by sequential treatment of **3b** and **3c** with *sec*-BuLi and Me_3SnCl. However, only complex mixtures were obtained from the indole-protected trisylhydrazone **3a** under the above experimental conditions, this result probably being a consequence of the competitive lithiation of the phenylsulfonyl substituent on the benzene ring. In order to have a broad variety of N-protected vinylstannanes, thus expanding their synthetic potentiality, the *N*-unsubstituted vinylstannane **1c** was converted (66–70% yield) into the *N*-oxymethyl derivatives **1d–f** by alkylation of the corresponding anion with MOM, MEM or SEM chloride, respectively. On the other hand, acylation of **1c** with di-*tert*-butyl dicarbonate gave the *N*-BOC derivative **1g** in 80% yield. It is worth mentioning that all attempts to alkylate or acylate **1c** with more electrophilic agents (BnBr, $PhSO_2Cl$, Tf_2O) caused the cleavage of

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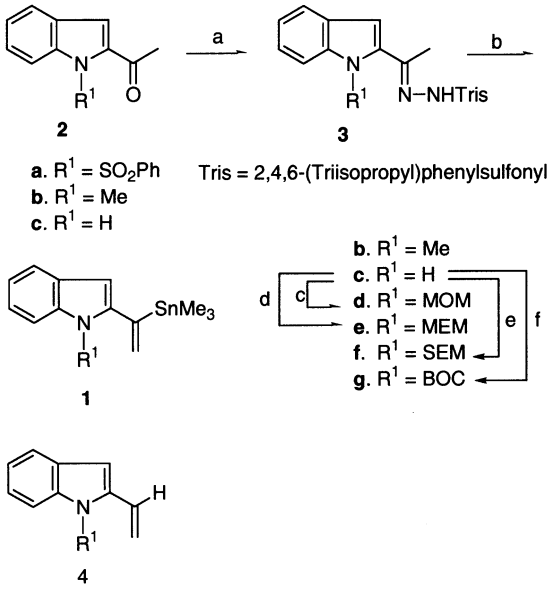
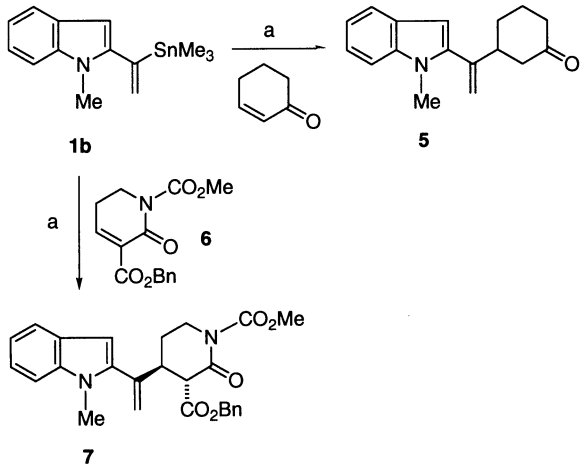


Scheme 2. *Reagents and conditions*: (a) Trisylhydrazide, HCl, CH_3CN, rt 14 h; (b) *sec*-BuLi, THF, −78 to 0°C, then Me_3SnCl, −78°C to rt, 2 h; (c) NaH, DMF, MOMCl, rt, 1 h; (d) NaH, DMF, MEMCl, rt, 1 h; (e) NaH, DMF, SEMCl, rt, 1 h; (f) $(BOC)_2O$, DMAP, CH_3CN, rt, 2.5 h.

the C–Sn bond to give 2-vinylindoles **4**. No reaction was observed with Me_3SiCl.

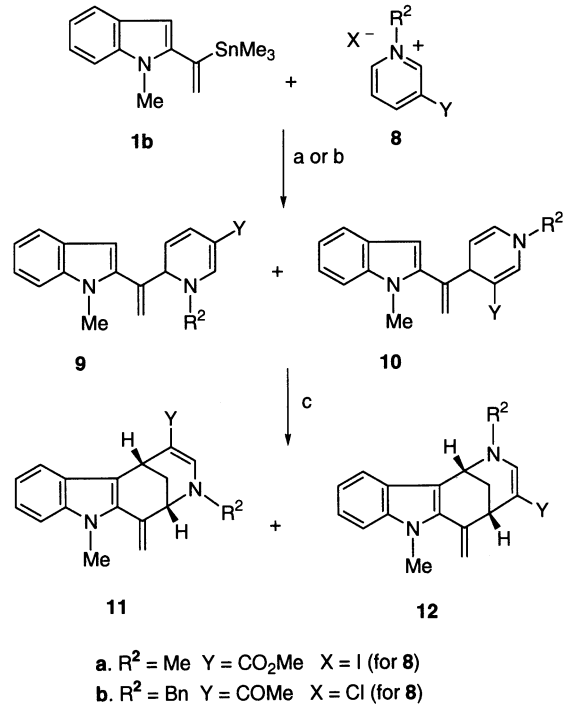
(*N*-Methylindolyl)vinylstannane **1b** was chosen to explore the Sn–Cu transmetallation step that would give an organocopper reagent able to undergo addition to *N*-alkylpyridinium salts. Although we had first considered generating the monovinylcopper species by direct reaction of **1b** with copper(I) salts under the conditions reported by Piers,[5b] the known poor capacity of these reagents to act as donors in intermolecular conjugate additions prompted us to study the direct conversion into the more reactive HO mixed alkyl vinyl cyanocuprate. This procedure takes advantage of ligand migration between HO cuprates and vinylstannanes, thus avoiding the normally required generation of the organolithium intermediates.[4] The transmetallation step was initially tested with simpler acceptors than pyridinium salts, such as 2-cyclohexenone[11] and the α,β-unsaturated lactam ester **6**[12] (Scheme 3). As expected, exposure of **1b** to 1 equiv. of $Me_2Cu(CN)Li_2$ in THF at rt presumably gave the mixed HO reagent, which upon addition of the above-mentioned acceptors selectively effected 1,4-addition of the vinyl residue to give **5** and **7** in 60 and 55% yields, respectively.

With this precedent, the HO mixed cyanocuprate derived from stannane **1b** was allowed to react with pyridinium salts **8**, which differ in the electron-withdrawing group (Y) at the β-position (Scheme 4, conditions a). As can be observed in Table 1 (entry 1), the transfer of the vinyl group took place mainly at the α-position (C-6) of 3-(methoxycarbonyl)pyridinium iodide **8a**. When the mixture of the initially formed α- and γ-adducts (**9a** and **10a**, respectively, not isolated) was treated with acid to promote cyclisation upon the indole ring, a 6:1 mixture of tetracycles **11a** and **12a** was obtained in 45% overall yield. When the same protocol was applied to 3-acetylpyridinium salt **8b**, tetracycle **11b**, coming from the initially formed α-adduct **9b**, was isolated as the unique reaction product in 35% yield (entry 2).



Scheme 3. *Reagents and conditions*: (a) $Me_2Cu(CN)Li_2$, THF, rt, 1.5 h, then 2-cyclohexenone or **6**, −78°C to rt, 1 h.

The tendency of this type of vinylcopper reagent to undergo addition at the α-position of the pyridine ring was not completely unexpected since it had previously been observed with the 'simplest' vinyl derivative, $(CH_2{=}CH)MeCu(CN)Li_2$.[7b] Furthermore, the structurally related HO mixed cyanocuprate derived from (phenylvinyl)stannane **13** reacted with pyridinium salt **8a** to give, after acylation of the crude mixture of dihydropyridines with trichloroacetic anhydride, a 4:1 mixture of 1,2-dihydropyridine **14a** and 1,4-dihydropyridine **15a** in 90%



Scheme 4. *Reagents and conditions*: (a) $Me_2Cu(CN)Li_2$, THF, rt, 1.5 h, then **8**, −30°C, 1 h; (b) MeLi, THF, −78°C, 15 min, $MgBr_2{\cdot}Et_2O$, 20 min, CuI, then **8**, −78°C to rt, 2 h; (c) $TsOH–C_6H_6$, THF, rt, 2 h.

Table 1. Reactions of vinylcopper reagents derived from vinylstannanes **1b** and **13** with pyridinium salts **8**

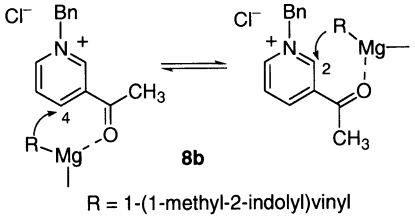
Entry	Stannane	Generation of vinylcopper[a]	Pyridinium salt	Products[b] (ratio)	Yield (%)
1	**1b**	a	**8a**	**11a**, **12a**, (6:1)	45
2	**1b**	a	**8b**	**11b**	35
3	**1b**	b	**8a**	**11a**, **12a**, (6:5)	60
4	**1b**	b	**8b**	**12b**	40
5	**13**	a	**8a**	**14a**, **15a**, (4:1)	90
6	**13**	a	**8b**	**15b**	30

[a] (a): $Me_2Cu(CN)Li_2$; (b): MeLi, $MgBr_2{\cdot}Et_2O$, CuI.
[b] After TsOH (from **1b**) or $(CCl_3CO)_2O$ (from **13**) treatment of the initially formed dihydropyridines.

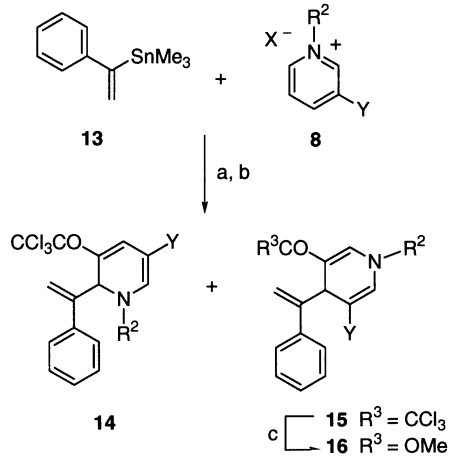
yield (Scheme 5 and Table 1, entry 5). However, when the same addition–acylation sequence was effected from 3-acetylpyridinium salt **8b**, only the corresponding 1,4-dihydropyridine **15b** was isolated, although in lower yield (30%, entry 6). This result might simply reflect the instability of the initially formed α-adduct under the acylation conditions rather than a change in the regioselectivity of the addition step. For practical reasons, **15b** was characterised as the bis(methoxycarbonyl)dihydropyridine **16b** after haloform reaction with MeONa in MeOH (see Section 4).

Interestingly, the α-regioselectivity in the indole series could be partially or totally reversed when pyridinium salts **8a** or **8b** were treated with the Cu-catalysed organomagnesium reagent derived from **1b** (Scheme 4, conditions b). Thus, the sequential treatment of vinylstannane **1b** with MeLi and $MgBr_2{\cdot}Et_2O$,[3a,b] and then with **8a** afforded a 6:5 mixture of tetracycles **11a** and **12a** in 60% yield after the acid-induced cyclisation step (Table 1, entry 3). On the other hand, tetracycle **12b**, coming from the γ-adduct **10b**, was isolated as the only product in 40% yield starting from 3-acetylpyridinium salt **8b** (entry 4). In these cases, the transfer of the vinyl group to the 4-position could be favoured by the initial coordination of the magnesium atom to the carbonyl oxygen of pyridinium salts **8** (**8b** in Scheme 6). The transfer of the vinyl group to the 2-position of the ring, also favoured for the same reasons, would probably be sterically hindered.

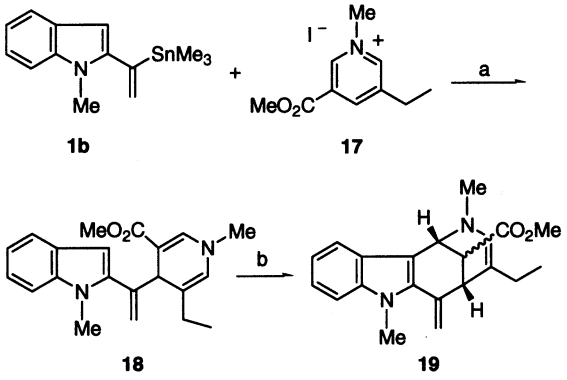
The structure of tetracycles **11** and **12** was unambiguously established by comparison of their NMR data with those corresponding to similar tetracycles lacking the vinyl group.[13] Thus, both regioisomers could be easily differentiated by the chemical shift values of protons and carbons at the bridgehead positions. The above addition–acid cyclisation sequence to give tetracycle **12b** represents a synthetic entry to the 1,5-methanoazocino[4,3-*b*]indole framework characteristic of the 2-vinylindole alkaloid uleine. In this synthetic context, when the above reaction sequence was extended to the 3,5-disubstituted pyridinium salt **17**,[14] the unstable tetracyclic enamine **19**, coming from 1,4-dihydropyridine **18**, was obtained as the major product in 30% yield (Scheme 7). The regioselectivity of the overall process deserves comment since it again involves the addition at the γ-position of the pyridine ring, followed by the cyclisation of the dihydropyridinium ion resulting from protonation of the vinylogous amide moiety.



Scheme 6.



Scheme 5. *Reagents and conditions*: (a) $Me_2Cu(CN)Li_2$, THF, rt, 1.5 h, then **8**, −30°C, 1 h; (b) $(CCl_3CO)_2O$, THF, 0°C, 2 h; (c) MeONa, MeOH, rt, 1 min.



Scheme 7. *Reagents and conditions*: (a) MeLi, THF, −78°C, 15 min, $MgBr_2{\cdot}Et_2O$, 20 min, CuI, then **17**, −78°C to rt, 2 h; (b) TsOH–C_6H_6, THF, rt, 3 h.

3. Conclusion

In summary, a series of 1-(2-indolyl)vinylstannanes **1**, diversely substituted at the indole nitrogen, has been efficiently prepared. From vinylstannane **1b**, two different 1-(2-indolyl)vinylcopper reagents have been generated for the first time, and their role in the addition-dihydropyridine cyclisation reaction sequence with *N*-alkylpyridinium salts **8** and **17** has been studied. Application of this protocol to the synthesis of 2-vinylindole alkaloids starting from *N*-protected indole derivatives **1d–f** is under active investigation.

4. Experimental

4.1. General methods

All nonaqueous reactions were performed under an argon atmosphere. All solvents were dried by standard methods. Reaction courses and product mixture were routinely monitored by TLC on silica gel (pre-coated F_{254} Merck plates). Drying of organic extracts during the workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of the solvents was accomplished under reduced pressure with a rotatory evaporator. Column and flash chromatography were carried out on neutral Al_2O_3 (Scharlau, Al835) and SiO_2 (silica gel 60, SDS, 0.04–0.06 mm), respectively. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 300 and 75.4 MHz, respectively, using TMS as an internal reference. Microanalyses and HRMS were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona.

4.2. General procedure for the preparation of trisylhydrazones 3

A mixture of the appropriate acetylindole **2**[15] (3 mmol), trisylhydrazide (3.1 mmol), and concentrated HCl (0.3 mL) in CH_3CN (3 mL) was stirred at rt overnight. The reaction mixture was cooled at 4°C for 2 h, and the precipitate was filtered to give pure **3** as a white solid.

4.2.1. 2-Acetyl-1-(phenylsulfonyl)indole trisylhydrazone (3a). Yield: 90%; mp 202–203°C; ^1H NMR δ 1.23 and 1.25 (2 d, J=6.9 Hz, 18H), 2.29 (s, 3H), 2.90 (m, 1H), 4.25 (m, 2H), 6.40 (s, 1H), 6.95 (m, 2H), 7.20–7.40 (m, 6H), 7.22 (s, 2H), 7.95 (s, 1H), 8.05 (d, J=8 Hz, 1H); ^{13}C NMR δ 18.6 (CH_3), 23.6 (CH_3), 24.7 (CH_3), 30.0 (CH), 34.3 (CH), 114.8 (CH), 115.9 (CH), 121.5 (CH), 123.8 (CH), 124.6 (CH), 125.7 (CH), 127.0 (CH), 128.5 (CH), 130.2 (C), 131.0 (C), 133.2 (CH), 135.6 (C), 137.5 (C), 139.1 (C), 147.5 (C), 151.8 (C), 153.4 (C). Anal. Calcd for $C_{31}H_{37}N_3O_4S_2$: C, 64.22; H, 6.43; N, 7.25. Found: C, 64.08; H, 6.68; N, 7.29.

4.2.2. 2-Acetyl-1-methylindole trisylhydrazone (3b). Yield: 80%; mp 154°C; ^1H NMR δ 1.24 (d, J=6.6 Hz, 6H), 1.28 (d, J=6.6 Hz, 12H), 2.25 (s, 3H), 2.90 (h, J=6.6 Hz, 1H), 3.61 (s, 3H), 4.25 (h, J=6.6 Hz, 2H), 6.75 (s, 1H), 7.10 (m, 1H), 7.19 (s, 2H), 7.25 (m, 2H), 7.55 (d, J=8 Hz, 1H), 7.95 (s, 1H); ^{13}C NMR δ 14.8 (CH_3), 23.5 (CH_3), 24.7 (CH_3), 29.8 (CH), 32.4 (CH_3), 34.2 (CH), 105.6 (CH), 109.7 (CH), 119.9 (CH), 121.0 (CH), 123.5 (CH), 123.8 (CH), 126.5 (C), 130.9 (C), 135.7 (C), 139.5 (C), 145.6 (C), 151.0 (2 C), 153.6 (C). Anal. Calcd for $C_{26}H_{35}N_3O_2S$: C, 68.84; H, 7.78; N, 9.26. Found: C, 68.76; H, 7.80; N, 9.24.

4.2.3. 2-Acetylindole trisylhydrazone (3c). Yield: 95%; mp 157°C; ^1H NMR δ 1.25 (d, J=6.9 Hz, 6H), 1.31 (d, J=6.9 Hz, 12H), 2.37 (s, 3H), 2.90 (h, J=6.9 Hz, 1H), 4.18 (h, J=6.9 Hz, 2H), 6.95 (s, 1H), 7.10 (m, 1H), 7.19 (s, 2H), 7.28 (m, 2H), 7.60 (d, J=8 Hz, 1H), 7.90 (br, 1H), 9.80 (br s, 1H). Anal. Calcd for $C_{25}H_{33}N_3O_2S{\cdot}1.5H_2O$: C, 64.35; H, 7.77; N, 9.00. Found: C, 64.17; H, 7.36; N, 8.92.

4.3. General procedure for the preparation of vinylstannanes 1b,c

To a cooled (−78°C) solution of trisylhydrazone **3** (0.45 mmol) in anhydrous THF (1 mL) was added dropwise a 1.3 M solution of *sec*-BuLi in THF (1.35 mmol for **3b** and 1.8 mmol for **3c**). After 30 min at −78°C, the resulting orange solution was slowly warmed to −20 to 0°C, during which time it turned dark brown. When the nitrogen evolution ceased, the reaction mixture was cooled again at −78°C followed by the dropwise addition of a 1 M solution of Me_3SnCl in THF (1.35 mmol for **3b** and 0.9 mmol for **3c**). After being allowed to warm to rt for 2 h, the reaction mixture was partitioned with H_2O and Et_2O, and extracted with Et_2O. The organic extracts were dried and concentrated to give crude **1b**,**c**. Column chromatography (Al_2O_3) gave pure **1b**,**c** as colorless oils. Owing to stability problems it was not possible to obtain microanalytically pure samples of **1**.

4.3.1. 1-Methyl-2-[1-(trimethylstannyl)vinyl]indole (1b). Elution with hexanes; 65%; ^1H NMR δ 0.23 (s, 9H), 3.66 (s, 3H), 5.74 (d, J=2.7 Hz, 1H), 6.04 (d, J=2.7 Hz, 1H), 6.21 (d, J=0.6 Hz, 1H), 7.07 (m, 1H), 7.17 (m, 1H), 7.26 (m, 1H), 7.54 (dm, 1H, J=7.5 Hz); ^{13}C NMR δ −8.63 (CH_3), 30.8 (CH_3), 99.7 (CH), 109.2 (CH), 119.5 (CH), 120.0 (CH), 121.0 (CH), 130.5 (CH_2), 128.5 (C), 138.2 (C), 144.8 (C).

4.3.2. 2-[1-(Trimethylstannyl)vinyl]indole (1c). Elution with 9:1 hexanes–AcOEt; 77%; ^1H NMR δ 0.32 (s, 9H), 5.43 (d, J=1.2 Hz, 1H), 6.11 (d, J=1.2 Hz, 1H), 6.36 (dd, J=0.9, 1.2 Hz, 1H), 7.06 (m, 1H), 7.14 (m, 1H), 7.31 (dd, J=8.1, 0.9 Hz, 1H), 7.55 (dd, J=8.1, 1.2 Hz, 1H), 8.15 (br s, 1H).

4.4. *N*-Protected stannanes 1d–f

A solution of stannane **1c** (1.5 mmol) in DMF (5 mL) was added dropwise to a suspension of NaH (55%, 1.65 mmol) in anhydrous THF (0.5 mL), and the resulting mixture was stirred at rt for 1 h. MOM, MEM or SEM chloride (1.65 mmol) was slowly added at 0°C, and the resulting solution was stirred at rt for 1 h. The reaction mixture was poured into H_2O–ice and extracted with Et_2O. The organic extracts were washed with H_2O (2×5 mL), dried, and concentrated to give crude **1d–f**. Column chromatography (Al_2O_3) gave pure **1d–f** as colorless oils.

4.4.1. 1-(Methoxymethyl)-2-[1-(trimethylstannyl)vinyl]-indole (1d). Elution with 98:2 hexanes–AcOEt; 70%; ^1H

NMR δ 0.22 (s, 9H), 3.34 (s, 3H), 5.40 (s, 2H), 5.75 (d, *J*=2.8 Hz, 1H), 6.16 (d, *J*=2.8 Hz, 1H), 6.26 (s, 1H), 7.08–7.23 (m, 2H), 7.42 (d, *J*=8.1 Hz, 1H), 7.42 (d, *J*=8.4 Hz, 1H).

4.4.2. 1-[(2-Methoxyethoxy)methyl]-2-[1-(trimethylstannyl)vinyl]indole (1e). Elution with hexanes; 70%; ^{1}H NMR δ 0.22 (s, 9H), 3.34 (s, 3H), 3.40 (m, 4H), 5.54 (s, 2H), 5.77 (d, *J*=2.4 Hz, 1H), 6.18 (d, *J*=2.4 Hz, 1H), 6.24 (s, 1H), 7.05–7.30 (m, 2H), 7.46 (dm, *J*=8 Hz, 1H), 7.55 (dm, *J*=8 Hz, 1H).

4.4.3. 1-{[(2-Trimethylsily)ethoxy]methyl}-2-[1-(trimethylstannyl)vinyl]indole (1f). Elution with hexanes; 66%; ^{1}H NMR δ 0.05 (s, 9H), 0.23 (s, 9H), 0.90 (t, *J*=8 Hz, 2H), 3.35 (t, *J*=8 Hz, 2H), 5.50 (s, 2H), 5.82 (d, *J*=2.8 Hz, 1H), 6.25 (d, *J*=2.8 Hz, 1H), 6.31 (s, 1H), 7.20–7.35 (m, 2H), 7.50 (dm, *J*=8 Hz, 1H), 7.60 (dm, *J*=8 Hz, 1H).

4.4.4. 1-(*tert*-Butoxycarbonyl)-2-[1-(trimethylstannyl)-vinyl]indole (1g). To a solution of stannane **1c** (0.5 g, 1.6 mmol) in CH_3CN (6 mL) was added DMAP (20 mg, 0.16 mmol) and di-*tert*-butyl dicarbonate (0.44 g, 1.9 mmol), and the mixture was stirred at rt for 2.5 h. The mixture was partitioned between H_2O and Et_2O and extracted with Et_2O. The organic extracts were dried and concentrated to give crude **1g**. Column chromatography (Al_2O_3, hexanes) gave pure **1g** (0.53 g, 80%) as a colorless oil: ^{1}H NMR δ 0.16 (s, 9H), 1.67 (s, 9H), 5.40 (d, *J*=3 Hz, 1H), 5.98 (d, *J*=3 Hz, 1H), 6.28 (s, 1H), 7.18–7.27 (m, 2H), 7.47 (dm, *J*=8.1 Hz, 1H), 7.94 (dm, *J*=7.8 Hz, 1H); ^{13}C NMR δ 28.4 (CH_3), 84.1 (C), 105.3 (CH), 115.5 (CH), 120.0 (CH), 122.7 (CH), 123.1 (CH), 125.3 (CH_2), 129.9 (C), 135.8 (C), 147.3, 149.5 (C), 150.8 (C).

4.4.5. Transmetallation between vinylstannane 1b and $Me_2Cu(CN)Li_2$ followed by reaction with 2-cyclohexenone and 6. CuCN (25 mg, 0.27 mmol) in anhydrous THF (0.3 mL) was treated with 1.6 M solution of MeLi in Et_2O (0.37 mL, 0.59 mmol) at 0°C for 10 min. The cooling bath was removed, and vinylstannane **1b** (0.1 g, 0.3 mmol) in THF (0.2 mL) was added. After 1.5 h at rt the dark red mixture was cooled to −78°C, and 2-cyclohexenone or **6**[16] (0.2 mmol) in THF (0.1 mL) was added rapidly. The resulting pale yellow mixture was allowed to warm to rt for 1 h. The reaction was quenched with H_2O and extracted with AcOEt. Solvent removal followed by flash chromatography of the residue (SiO_2, hexanes–AcOEt) gave vinylindoles **5** and **7** as amorphous solids.

4.4.6. 3-[1-(1-Methyl-2-indolyl)vinyl]cyclohexanone (5). Elution with 85:15 hexanes–AcOEt; 60%; ^{1}H NMR δ 1.65 (m, 2H), 2.04 (m, 2H), 2.38 (m, 3H), 2.58 (m, 1H), 2.85 (m, 1H), 3.67 (s, 3H), 5.21 (s, 1H), 5.43 (s, 1H), 6.37 (d, *J*=0.9 Hz, 1H), 7.10 (m, 1H), 7.22 (m, 1H), 7.31 (dd, *J*=7.8, 0.9 Hz, 1H), 7.59 (dm, *J*=8 Hz, 1H); ^{13}C NMR δ 24.9 (CH_2), 30.5 (CH_2), 30.8 (CH_3), 41.2 (CH_2), 45.0 (CH), 46.5 (CH_2), 100.9 (CH), 109.5 (CH), 116.7 (CH_2), 119.8 (CH), 120.4 (CH), 121.7 (CH), 127.5 (C), 137.8, 140.2 (C), 143.5 (C), 210.8 (C); HRMS calcd for $C_{17}H_{19}NO$ 253.1460, found 253.1466.

4.4.7. *trans*-3-(Benzyloxycarbonyl)-4-[1-(1-methyl-2-indolyl)vinyl]-1-(methoxycarbonyl)-2-piperidone (7). Elution with 7:3 hexanes–AcOEt; 55%; ^{1}H NMR (assignment aided by ^{1}H–^{1}H COSY and HMQC) δ 1.76 (m, 1H, 5-H), 2.14 (m, 1H, 5-H), 3.38 (td, *J*=10.8, 10.5, 6.3 Hz, 1H, 4-H), 3.59 (s, 3H, NMe), 3.63 (m, 1H, 6-H), 3.76 (d, *J*=10.8 Hz, 1H, 3-H), 3.85 (m, 1H, 6-H), 3.86 (s, 3H, OMe), 5.07 and 5.15 (2d, *J*=12 Hz, OCH_2, 2H), 5.22 (s, 1H, $=CH_2$), 5.44 (s, 1H, $=CH_2$), 6.41 (s, 1H, indole 3-H), 7.12 (m, 1H, indole), 7.27 (m, 7H, Ar), 7.56 (d, *J*=7.8 Hz, 1H, indole 4-H); ^{13}C NMR (assignment aided by HMQC) δ 27.6 (C-5), 30.8 (NMe), 42.6 (C-4), 45.2 (C-6), 54.2 (OMe), 56.3 (C-3), 67.5 (CH_2Ph), 101.9 (indole C-3), 109.6 (indole C-7), 118.2 ($=CH_2$), 119.9 (indole C-4), 120.6 (indole C-5), 122.1 (indole C-6), 127.4 (indole C-3a), 128.3 (5C, complex signal, Ph), 135.2 (C, Ph), 138.1, 138.7 (2C, C-2 and C-7a), 140.6 (C=), 154.5, 166.9, 168.6 (3C, CO); HRMS calcd for $C_{26}H_{26}N_2O_5$ 446.1849, found 446.1841.

4.4.8. Transmetallation between vinylstannane 1b and $Me_2Cu(CN)Li_2$ followed by reaction with pyridinium salt 8a. Vinylstannane **1b** (0.25 g, 0.8 mmol) was transmetallated according to the above experimental procedure. Pyridinium salt **8a** (112 mg, 0.4 mmol) was added rapidly upon the dark red reaction mixture at −78°C, followed by addition of anhydrous THF (5 mL). The mixture was allowed to rise to −30°C, stirred at this temperature for 1 h, quenched with H_2O, and extracted with Et_2O. After solvent removal, the resulting residue was dissolved in anhydrous THF (10 mL), treated at −20°C with enough of a saturated C_6H_6 solution of TsOH to bring the pH to 3.5–4. The resulting mixture was allowed to rise to rt, stirred for 2 h, poured into saturated aqueous Na_2CO_3, and extracted with Et_2O. Concentration of the extracts followed by column chromatography (Al_2O_3, 9:1 hexanes–AcOEt) gave a 6:1 mixture of tetracycles **11a** and **12a** (56 mg, 45%). An additional column chromatography (Al_2O_3, 9:1 hexanes–AcOEt) gave pure *methyl 3,11-dimethyl-1-methylene-1,2,3,6-tetrahydro-2,6-methanoazocino[4,5-b]indole-5-carboxylate* (**11a**): ^{1}H NMR δ 1.91 (dm, *J*=12.3 Hz, 1H), 2.18 (dm, *J*=12.3 Hz, 1H), 3.03 (s, 3H), 3.67 (s, 3H), 3.80 (br s, 1H), 3.87 (s, 3H), 4.38 (br s, 1H), 5.02 and 5.51 (2 s, 2H), 7.15 (m, 1H), 7.23 (m, 3H), 8.01 (d, *J*=8.1 Hz, 1H); ^{13}C NMR δ 23.8 (CH), 29.3 (CH_2), 32.5 (CH_3), 40.9 (CH_3), 50.4 (CH_3), 61.6 (CH), 100.0 (C), 107.7 (CH_2), 108.5 (CH), 119.3 (CH), 121.0 (CH), 121.5 (C), 123.0 (CH), 124.5 (C), 130.4 (C), 136.7, 139.2 (C), 143.9 (CH), 167.3 (C); HRMS calcd for $C_{19}H_{20}N_2O_2$ 308.1524, found 308.1519. Anal. Calcd for $C_{19}H_{20}N_2O_2.3/4H_2O$: C, 70.90; H, 6.73; N, 8.70. Found: C, 70.60; H, 6.43; N, 8.45.

4.4.9. 5-Acetyl-3-benzyl-11-methyl-1-methylene-1,2,3,6-tetrahydro-2,6-methanoazocino[4,5-*b*]indole (11b). Operating as above, from vinylstannane **1b** (0.25 g, 0.8 mmol) and pyridinium salt **8b** (0.1 g, 0.4 mmol), tetracycle **11b** (51 mg, 35%) was obtained after column chromatography (Al_2O_3, 75:25 hexanes–AcOEt): ^{1}H NMR δ 1.81 (dm, *J*=12 Hz, 1H), 2.09 (s, 3H), 2.20 (dm, *J*=12 Hz, 1H), 3.84 (s, 3H), 3.89 (br s, 1H), 4.42 (d, *J*=15.6 Hz, 1H), 4, 54 (d, *J*=15.6 Hz, 1H), 4.69 (br s, 1H), 4.94 and 5.45 (2 s, 2H), 7.10 (m, 1H), 7.21–7.45 (m, 8H), 8.10 (d, *J*=8 Hz, 1H); ^{13}C NMR δ 22.4 (CH_3), 23.6

(CH), 29.3 (CH_2), 32.3 (CH_3), 56.9 (CH_2), 58.9 (CH), 107.9 (CH_2), 108.3 (CH), 115.0 (C), 119.5 (CH), 121.6 (CH, C), 123.2 (CH), 124.7 (C), 127.1, 127.9, 129.0 (CH), 130.3 (C), 136.7, 137.1, 139.2 (C), 145.7 (CH), 190.7 (C); HRMS calcd for $C_{25}H_{24}N_2O$ 368.1888, found 368.1872.

4.4.10. Copper(I)-catalysed reaction of Grignard reagent derived from 1b with pyridinium salt 8a. Vinylstannane **1b** (114 mg, 0.36 mmol) in anhydrous THF (1 mL) was treated with a 1.6 M solution of MeLi in Et_2O (0.27 mL, 0.43 mmol) at −78°C for 15 min. To the resulting yellow solution solid $MgBr_2{\cdot}Et_2O$ (93 mg, 0.36 mmol) was added at −78°C and, after 20 min, solid CuI (20 mg). After 10 min, pyridinium salt **8a** (0.3 mmol) was added upon the colorless mixture, followed by addition of anhydrous THF (3 mL). The mixture was allowed to rise to rt (2 h), quenched with H_2O and extracted with Et_2O. After solvent removal, the resulting residue was dissolved in anhydrous THF (10 mL), and treated as above with TsOH–C_6H_6. After workup, the resulting residue was chromatographed (Al_2O_3). On elution with 9:1 hexanes–AcOEt, *methyl 2,7-dimethyl-6-methylene-1,2,5,6-tetrahydro-1,5-methanoazocino[4,3-b]indole-4-carboxylate* (**12a**) was obtained: 25 mg (27%); ^{1}H NMR δ 1.95 (dt, J=12.3, 3.3 Hz, 1H), 2.16 (dt, J=12.3, 2.4 Hz, 1H), 3.15 (s, 3H), 3.66 (s, 3H), 3.66 (masked, 1H), 3.88 (s, 3H), 4.55 (br s, 1H), 5.37 and 5.43 (2 s, 2H), 7.05–7.35 (m, 3H), 7.62 (d, J=8.1 Hz, 1H); ^{13}C NMR δ 29.9 (CH_2), 32.5 (CH_3), 36.2 (CH), 42.3 (CH_3), 49.4 (CH), 50.4 (CH_3), 97.8 (C), 108.3 (CH_2), 109.2 (CH), 112.9 (C), 118.4 (CH), 119.7 (CH), 122.4 (CH), 125.2 (C), 135.1 (C), 138.8 (C), 141.2 (C), 144.3 (CH), 167.8 (C); HRMS calcd for $C_{19}H_{20}N_2O_2$ 308.1524, found 308.1518. On elution with 85:15 hexanes–AcOEt, tetracycle **11a** was obtained: 31 mg (33%).

4.4.11. 4-Acetyl-2-benzyl-7-methyl-6-methylene-1,2,5,6-tetrahydro-1,5-methanoazocino[4,3-*b*]indole (12b). Operating as above, from vinylstannane **1b** (114 mg, 0.36 mmol) and pyridinium salt **8b** (75 mg, 0.3 mmol) tetracycle **12b** (45 mg, 40%) was obtained after column chromatography (Al_2O_3, 65:35 hexanes–AcOEt): ^{1}H NMR δ 1.85 (dt, J=12, 3 Hz, 1H), 2.13 (s, 3H), 2.14 (dt, J=12, 2.7 Hz, 1H), 3.88 (s, 3H), 3.95 (br s, 1H), 4.42 (d, J=15.3 Hz, 1H), 4.62 (br s, 1H), 4.72 (d, J=15.3 Hz, 1H), 5.41 and 5.55 (2s, 2H), 7.15 (m, 1H), 7.26–7.50 (m, 7H), 7.58 (d, J=8.1 Hz, 1H); ^{13}C NMR δ 24.2 (CH_3), 29.5 (CH_2), 32.5 (CH_3), 34.9 (CH), 46.9 (CH), 58.9 (CH_2), 109.1 (CH_2), 109.2 (CH), 111.6 (C), 112.6 (C), 118.0 (CH), 119.8 (CH), 122.4 (CH), 124.9 (C), 127.3, 128.9, 127.9 (CH), 135.3 (C), 136.5 (C), 138.7 (C), 140.2 (C), 145.7 (CH), 191.9 (C); HRMS calcd for $C_{25}H_{24}N_2O$ 368.1888, found 368.1876.

4.4.12. Methyl 4-ethyl-2,7-dimethyl-6-methylene-1,2,5,6-tetrahydro-1,5-methanoazocino[4,3-*b*]indole-12-carboxylate (19). Operating as above, from vinylstannane **1b** (187 mg, 0.47 mmol) and pyridinium salt **17**[17] (120 mg, 0.39 mmol) tetracycle **19** (38 mg, 30%, unstable) was obtained after column chromatography (Al_2O_3, 7:3 hexanes–AcOEt): ^{1}H NMR δ 1.03 (t, J=6.6 Hz, 3H), 2.01 (qd, J=6.6, 1.2 Hz, 2H), 2.72 (s, 3H), 3.09 (t, J=2.7 Hz, 1H), 3.26 (dd, J=2.4, 1.2 Hz, 1H), 3.52 (s, 3H), 3.87 (s, 3H), 4.84 (br s, 1H), 5.09 (s, 1H), 5.41 (d, J=1.2 Hz, 1H), 5.44 (s, 1H), 7.05–7.25 (m, 3H), 7.67 (dm, J=8 Hz, 1H); ^{13}C NMR δ 13.0 (CH_3), 25.1 (CH_2), 32.6 (CH_3), 41.7 (CH_3), 42.9 (CH), 45.6 (CH), 50.6 (CH), 51.7 (CH_3), 107.7 (CH_2), 108.9 (CH), 109.2 (C), 112.7 (C), 119.5 (CH), 119.6 (CH), 122.4 (CH), 126.5 (C), 135.1 (C), 138.4 (C), 139.0 (C), 172.0 (C).

4.4.13. Transmetallation between vinylstannane 13 and $Me_2Cu(CN)Li_2$ followed by reaction with pyridinium salt 8a. Vinylstannane **13**[18] (0.38 g, 1.43 mmol) and $Me_2Cu(CN)Li_2$ (1.43 mmol) in anhydrous THF (1.5 mL) were transmetallated according to the procedure described for **1b**. Pyridinium salt **8a** (0.2 g, 0.71 mmol) was added upon the reaction mixture at −30°C followed by addition of anhydrous THF (15 mL). The mixture was stirred at −30°C for 1.5 h, quenched with H_2O and extracted with Et_2O. After solvent removal, the resulting residue was dissolved in THF (15 mL), and treated with trichloroacetic anhydride at 0°C for 2 h. The reaction mixture was poured into aqueous Na_2CO_3, and extracted with Et_2O. Concentration of the extracts followed by flash chromatography (SiO_2, 85:15 hexanes–AcOEt) gave a 4:1 mixture of dihydropyridines **14a** and **15a** (0.26 g, 90%). An additional chromatography (SiO_2, 85:15 hexanes–AcOEt) gave pure *1-methyl-5-(methoxycarbonyl)-2-(1-phenylvinyl)-3-(trichloroacetyl)-1,2-dihydropyridine* (**14a**): 160°C (Et_2O–acetone); ^{1}H NMR δ 3.01 (s, 3H), 3.76 (s, 3H), 5.40 (s, 1H), 5.40 and 5.58 (2s, 2H), 7.20–7.50 (m, 5H), 7.58 (s, 1H), 8.40 (s, 1H); ^{13}C NMR δ 44.2 (CH_3), 51.8 (CH_3), 62.2 (CH), 95.4 (C), 96.9 (C), 107.9 (C), 118.6 (CH_2), 127.0 (CH), 127.4 (CH), 128.4 (CH), 139.0 (CH), 140.2 (C), 146.2 (C), 151.7 (CH), 166.8 (C), 178.3 (C). Anal. Calcd for $C_{18}H_{16}Cl_3NO_3$: C, 53.96; H, 4.02; N, 3.50. Found: C, 53.98; H, 4.02; N, 3.50.

4.4.14. 3-Acetyl-1-benzyl-5-(methoxycarbonyl)-4-(1-phenylvinyl)-1,4-dihydropyridine (16b). Operating as above, from vinylstannane **13** (0.43 g, 1.6 mmol), and pyridinium salt **8b** (0.2 g, 0.8 mmol) crude dihydropyridine **15b** (145 mg, 30%) was obtained after flash chromatography (SiO_2, 9:1 hexanes–AcOEt). Dihydropyridine **15b** was allowed to react with MeONa (0.8 mmol) in MeOH (15 mL) at rt for 1 min. The solvent was removed and the resulting residue was partitioned between H_2O and Et_2O, and extracted with Et_2O. After concentration of the ethereal extracts, the resuting residue was chromatographed (flash, SiO_2, 8:2 hexanes–AcOEt) to give dihydropyridine **16b**: 107 mg (90%); ^{1}H NMR δ 2.15 (s, 3H), 3.49 (s, 3H), 4.52 (s, 2H), 4.92 (s, 1H), 5.07 and 5.19 (2s, 2H), 7.08 (s, 1H), 7.10–7.40 (m, 11H); ^{13}C NMR δ 25.3 (CH_3), 36.9 (CH), 51.1 (CH_3), 58.3 (CH_2), 109.6 (C), 115.8 (CH_2), 118.3 (C), 127.0–129.1 (complex), 137.6 (CH), 138.9 (CH), 154.6 (C), 167.4 (C), 195.1 (C); HRMS calcd for $C_{24}H_{23}NO_3$ 377.1677, found 377.1673.

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