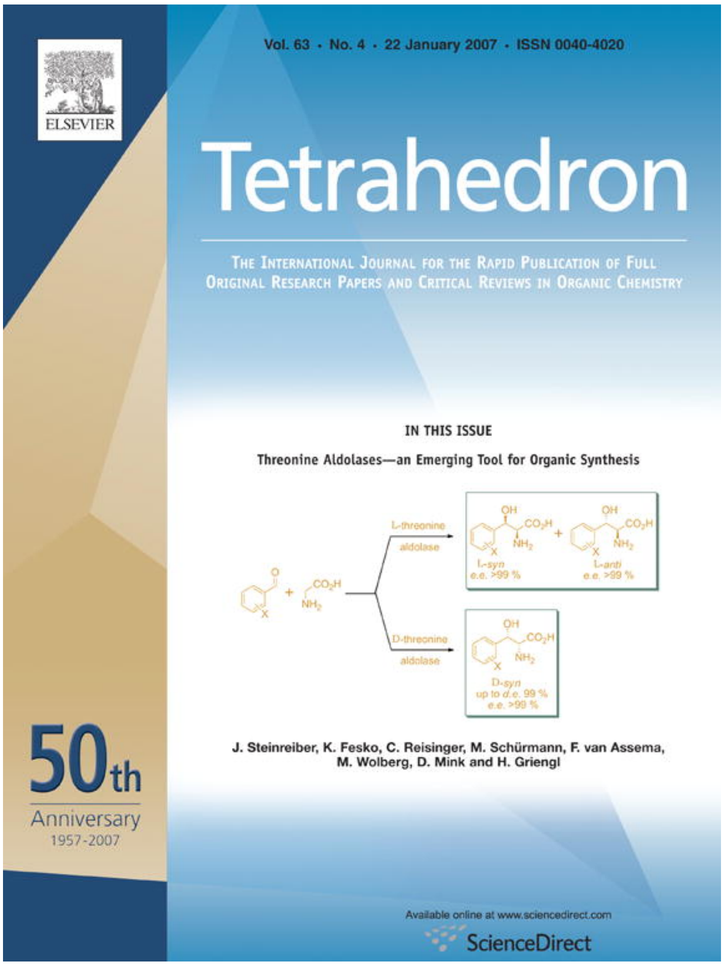
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Facile synthesis of azocino[4,3-*b*]indoles by ring-closing metathesis

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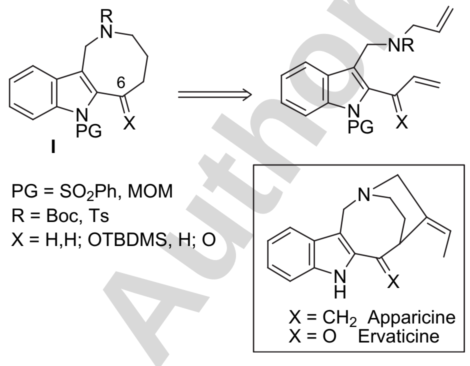
Abstract—The azocino[4,3-*b*]indole system, tricyclic substructure of the indole alkaloids apparicine and ervaticine, is efficiently assembled by ring-closing metathesis of 2-allyl-3-(allylaminomethyl)indoles. The metathesis sites are introduced into the indole nucleus by reductive amination of a 3-formyl derivative with allylamine, followed by α-lithiation with subsequent electrophilic trapping with acrolein.

1. Introduction

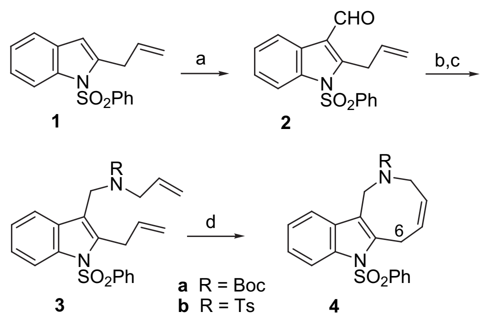
Ruthenium-catalyzed ring-closing metathesis (RCM)[1] has emerged as a powerful tool for the construction of a great variety of carbo- and heterocycles from acyclic precursors.[2] In particular, the RCM methodology has turned out to be very useful for the synthesis of medium-sized rings,[3] which is generally problematic due to disfavored entropic factors and transannular interactions. Our interest in the development of indole annulation methodologies led us to consider RCM reactions of indole-containing dienes[4,5] for the efficient construction of medium-sized indolo 2,3-fused carbo- and azacycles, which are common structural arrangements in many natural and synthetic bioactive compounds.[6] In this paper we report a direct synthetic approach to the azocino[4,3-*b*]indole system **I** by RCM of appropriate 2,3-dialkenylindoles incorporating a nitrogen atom in the tether linking the two double bonds (Scheme 1). It should be noted that **I** constitutes the tricyclic substructure of apparicine,[7] an indole alkaloid known for 40 years but still awaiting its first total synthesis,[8] and also the unprecedented 2-acylindole analogue ervaticine.[9]



Scheme 1. Synthetic plan.

2. Results and discussion

We set out to explore the feasibility of the protocol using model RCM precursors unfunctionalized at the benzylic indole α-position, such as 2-allyl-3-(allylaminomethyl)-indoles **3**.[10] For the preparation of these substrates, a fast formylation–reductive amination sequence starting from the known 2-allylindole **1**[11] was envisaged (Scheme 2). A strong electron-withdrawing benzenesulfonyl group was placed at the indole nitrogen to guarantee the stability of the proposed gramine-type intermediates. Thus, Friedel–Crafts reaction of **1** with Cl_2CHOMe in the presence of $TiCl_4$ gave the aldehyde **2** (90%), which was subjected to reductive amination with allylamine, followed by reaction of the resulting secondary amine with $(t\text{-BuOCO})_2O$ or TsCl. In this manner, the required RCM substrates **3a** or **3b**, bearing different



Scheme 2. Reagents and conditions: (a) Cl_2CHOMe, $TiCl_4$, CH_2Cl_2, −78 °C, 2 h, 90%; (b) allylamine, $NaBH(OAc)_3$, AcOH, rt, overnight; (c) $(t\text{-BuOCO})_2O$, 4:1 MeOH–Et_3N, reflux, 4 h, 65% (**3a**) or TsCl, Et_3N, CH_2Cl_2, rt, overnight 65% (**3b**); (d) $(PCy_3)_2(Cl)_2Ru{=}CHPh$, CH_2Cl_2, reflux, overnight, 60% (**4a**), 89% (**4b**).

Keywords: Ring-closing metathesis; Indole; Indole alkaloids.
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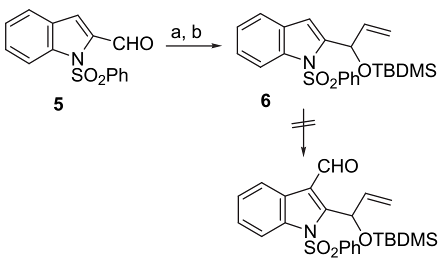
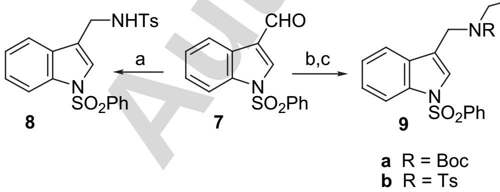
protecting groups at the aliphatic nitrogen, were obtained in 65% overall yield from **2**. Satisfactorily, ring closure of the *N*-Boc diene **3a** took place in refluxing dichloromethane in the presence of the first generation Grubbs catalyst to give the azocino[4,3-*b*]indole **4a** in 60% yield. The *N*-tosyl derivative **3b** proved to be a better substrate as it led to **4b** in a higher yield (89%).

With model azocino[4,3-*b*]indoles in hand, we sought to elaborate C-6 functionalized derivatives simply by extending the chemistry outlined above to an *O*-protected 2-(1-hydroxyallyl)indole. To this end, we selected silyl ether **6**, which was easily prepared from aldehyde **5**,[12] by reaction with vinylmagnesium bromide followed by protection of the resulting alcohol with *tert*-butyldimethylsilyl chloride (63% overall yield, Scheme 3). Disappointingly, we were not able to introduce the formyl group needed for the reductive amination step since **6** gave only a complex mixture upon subjection to the above Friedel–Crafts protocol.



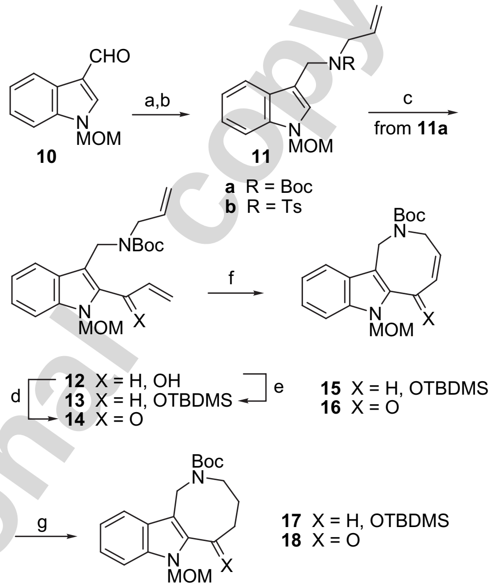
Scheme 3. Reagents and conditions: (a) BrMgCH=CH_2, THF, −78 °C–rt, overnight; (b) TBDMSCl, DMF, imidazole, 55 °C, overnight, 63%.

This unsuccessful result prompted us to change the order of the synthetic steps. Functionalization at the 2-position of a properly 3-substituted indole by α-metalation followed by electrophilic trapping seemed to be the logical solution. With this aim, we focused our attention on 3-(aminomethyl)-indoles **8** and **9**, which were available from indole-3-carbaldehyde **7**[13] through reductive amination techniques, using tosylamine or, as above, allylamine followed by acylation (Scheme 4). Unfortunately, treatment of these substrates with either LDA, *sec*-BuLi or *tert*-BuLi in THF under a variety of experimental conditions, followed by addition of DMF, HCOOMe, or acrolein led to the recovery of the starting product.



Scheme 4. Reagents and conditions: (a) $TsNH_2$, toluene, reflux, 24 h, then $NaBH_4$, MeOH, rt, 24 h, 70%; (b) allylamine, $NaBH(OAc)_3$, AcOH, rt, overnight; (c) $(t\text{-BuOCO})_2O$, 4:1 MeOH–Et_3N, reflux, 4 h, 68% (**9a**) or TsCl, Et_3N, CH_2Cl_2, rt, overnight 67% (**9b**).

We reasoned that the replacement of the indole protecting group by a methoxymethyl (MOM) group could facilitate the α-lithiation, despite a probable reduction in stability of some synthetic intermediates due to the lower electron-withdrawing character of this moiety. Thus, we turned to aldehyde **10**[14] (Scheme 5), which was converted into the allylaminomethyl derivatives **11** under the usual conditions. As the tosyl compound **11b** partially decomposed under chromatographic purification, we decided to continue the synthesis only with the more stable *N*-Boc derivative **11a**, which could be isolated in a reproducible 72% yield.



Scheme 5. Reagents and conditions: (a) allylamine, $NaBH(OAc)_3$, AcOH, rt, overnight; (b) $(t\text{-BuOCO})_2O$, 4:1 MeOH–Et_3N, reflux, 4 h, 72% (**11a**) or TsCl, Et_3N, CH_2Cl_2, rt, overnight (**11b**); (c) *t*-BuLi, THF, −78 °C, 2 h, then acrolein, −78 °C, 3.5 h, 79%; (d) MnO_2, CH_2Cl_2, rt, 60 h, 64%; (e) TBDMSCl, DMF, imidazole, 55 °C, overnight, 64%; (f) $(PCy_3)_2(Cl)_2Ru$=CHPh, CH_2Cl_2, reflux, overnight, 85% (**15**) or $(Im)(PCy_3)(Cl)_2Ru$=CHPh, CH_2Cl_2, rt, overnight, 86% (**16**); (g) H_2, Pd/C, MeOH, 12 h, 80% (**17**), 82% (**18**).

We were pleased to find that the desired α-lithiation did take place from **11a** upon treatment with *tert*-BuLi in THF at −78 °C. After quenching with acrolein, the unstable alcohol **12** was isolated (79%) and immediately protected as the *tert*-butyldimethylsilyl ether **13** (64%) or, alternatively, oxidized with MnO_2 (64%) to the ketone **14**. Satisfactorily, when **13** was subjected to the previously used RCM conditions (first generation Grubbs catalyst in refluxing dichloromethane) the expected tricyclic compound **15** was obtained in good yield (85%). However, no cyclization was observed from ketone **14** under the above protocol, probably due to the presence of an electron-poor double bond, and only dimeric products coming from intermolecular metathesis reactions were formed. This problem was circumvented simply by using the more efficient second generation Grubbs catalyst at room temperature, leading to tricyclic ketone **16** in 86% yield. Finally, the saturated forms of the eight-membered heterocycles **17** and **18** were obtained by catalytic hydrogenation over Pd/C.

3. Conclusion

We have developed a new synthetic route to the azocino[4,3-*b*]indole system[15,16] relying on RCM of 2-allyl-3-(allylaminomethyl)indoles. The efficiency of the cyclization combined with the easy preparation of the dienic precursors from simple indolic derivatives make this strategy attractive for the construction of medium-sized indolo 2,3-fused carbo- and azacycles, which are scaffolds found in many bioactive compounds.

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 mixtures were routinely monitored by TLC on silica gel (precoated F_{254} Merck plates). Drying of organic extracts was carried out over anhydrous Na_2SO_4. The solvents were evaporated under reduced pressure with a rotary evaporator. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.04–0.06 mm). Melting points are uncorrected. Unless otherwise indicated, NMR spectra were recorded in $CDCl_3$ at 300 MHz (^{1}H) or 75.4 MHz (^{13}C) using Me_4Si as an internal reference.

4.1.1. 2-Allyl-1-(phenylsulfonyl)-3-indolecarbaldehyde (2). 2-Allylindole **1**[11] (0.7 g, 2.3 mmol) in CH_2Cl_2 (6 mL) was added to a solution of $TiCl_4$ (0.51 mL, 4.7 mmol) and Cl_2CHOCH_3 (0.4 mL, 4.7 mmol) in CH_2Cl_2 (6 mL) at −78 °C, and the resulting mixture was stirred at −78 °C for 2 h. The reaction mixture was diluted with H_2O, basified with 10% aqueous Na_2CO_3, and extracted with CH_2Cl_2. The organic extracts were dried and concentrated and the residue was purified by flash chromatography (9:1 hexanes–AcOEt) to give aldehyde **2**: 0.69 g (90%); ^{1}H NMR δ 4.22 (m, 2H), 5.05 (dm, J=17.0, 1.1 Hz, 1H), 5.12 (dm, J=10.0, 1.1 Hz, 1H), 6.05 (m, 1H), 7.34–7.65 (m, 5H), 7.86 (m, 2H), 8.17 (m, 1H), 8.22 (m, 1H), 10.26 (s, 1H); ^{13}C NMR δ 29.5 (CH_2), 114.3 (CH), 117.6 (CH_2), 119.5 (C), 121.4 (CH), 125.1 (CH), 125.6 (CH), 126.0 (C), 126.6 (2CH), 129.4 (2CH), 134.2 (CH), 134.4 (CH), 135.9 (C), 138.4 (C), 148.8 (C), 185.6 (CO). Anal. Calcd for $C_{18}H_{15}NO_3S\cdot 1/4H_2O$: C, 65.52%; H, 4.73%; N, 4.24%. Found: C, 65.81%; H, 4.86%; N, 4.12%.

4.1.2. 2-Allyl-3-[(*N*-allyl-*N*-*tert*-butoxycarbonylamino)-methyl]-1-(phenylsulfonyl)indole (3a). Allylamine (0.15 mL, 2.0 mmol), $NaBH(OAc)_3$ (0.64 g, 3.0 mmol), and AcOH (0.06 mL, 1.1 mmol) were successively added to aldehyde **2** (0.33 g, 1.0 mmol) in CH_2Cl_2 (8 mL), and the mixture was stirred at rt overnight. The reaction mixture was diluted with H_2O, basified with solid Na_2CO_3, and extracted with CH_2Cl_2. The organic extracts were dried and concentrated and the resulting residue was purified by flash chromatography (98:2 CH_2Cl_2–MeOH) to give the secondary amine: 0.32 g. This compound was dissolved in MeOH (8 mL), treated with Et_3N (2 mL) and $(t\text{-BuOCO})_2O$ (0.32 g, 1.46 mmol), and the resulting mixture was heated at reflux for 4 h. The solvent was removed and the residue was dissolved in CH_2Cl_2 (15 mL) and washed successively with 1 N HCl and brine. The organic extracts were dried and concentrated and the residue was purified by flash chromatography (CH_2Cl_2) to give **3a**: 0.30 g (65%); ^{1}H NMR (5:1 mixture of rotamers, major rotamer) δ 1.49 (s, 9H), 3.40 (br s, 2H), 3.83 (br d, J=6.0 Hz, 2H), 4.55 (s, 2H), 4.90 (m, 2H), 5.01 (m, 2H), 5.60 (m, 1H), 5.95 (m, 1H), 7.20–7.65 (m, 6H), 7.70 (m, 2H), 8.20 (d, J=7.5 Hz, 1H); ^{13}C NMR (major rotamer) δ 28.4 (3CH_3), 29.9 (CH_2), 38.5 (CH_2), 47.0 (CH_2), 79.9 (C), 115.0 (CH), 115.9 (CH_2), 116.2 (CH_2), 119.3 (CH), 123.7 (CH), 124.5 (CH), 126.2 (2CH), 129.0 (2CH), 129.8 (C), 133.4 (CH), 133.5 (CH), 134.9 (CH), 136.5 (C), 136.9 (C), 138.7 (C), 155.5 (CO); HRMS calcd for $C_{26}H_{30}N_2O_4S$ 466.1926, found 466.1932.

4.1.3. 2-Allyl-3-[(*N*-allyl-*N*-tosylamino)methyl]-1-(phenylsulfonyl)indole (3b). Aldehyde **2** (0.33 g, 1.0 mmol) was allowed to react as above with allylamine and the resulting secondary amine (0.32 g) was dissolved in CH_2Cl_2 (10 mL) and treated with tosyl chloride (0.19 g, 1.0 mmol) and Et_3N (0.14 mL, 1.0 mmol) at rt overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with 1 N HCl and brine. The organic extracts were dried and concentrated and the residue was chromatographed (flash, CH_2Cl_2) to give **3b**: 0.34 g (65%); mp 118 °C (Et_2O); ^{1}H NMR δ 2.44 (s, 3H), 3.52 (d, J=6.3 Hz, 2H), 3.76 (dm, J=6.0 Hz, 2H), 4.36 (s, 2H), 4.66 (dd, J=17.0, 1.5 Hz, 1H), 4.72 (dd, J=10.0, 1.5 Hz, 1H), 4.92 (dd, J=17.0, 1.5 Hz, 1H), 4.99 (dd, J=10.0, 1.5 Hz, 1H), 5.23 (m, 1H), 5.93 (m, 1H), 7.25–7.75 (m, 12H), 8.20 (d, J=7.5 Hz, 1H); ^{13}C NMR δ 21.5 (CH_3), 29.9 (CH_2), 41.5 (CH_2), 49.4 (CH_2), 114.9 (CH), 115.5 (C), 116.3 (CH_2), 118.1 (CH_2), 119.5 (CH), 123.8 (CH), 124.7 (CH), 126.2 (2CH), 127.2 (2CH), 129.0 (2CH), 129.1 (C), 129.7 (2CH), 132.4 (CH), 133.6 (CH), 134.7 (CH), 136.5 (C), 137.2 (C), 139.2 (C), 139.7 (C), 143.4 (C). Anal. Calcd for $C_{28}H_{28}N_2O_4S_2$: C, 64.59%; H, 5.41%; N, 5.38%. Found: C, 64.67%; H, 5.43%; N, 5.35%.

4.1.4. 2-(*tert*-Butoxycarbonyl)-7-(phenylsulfonyl)-1,2,3,6-tetrahydroazocino[4,3-*b*]indole (4a). $(PCy_3)_2(Cl)_2Ru{=}CHPh$ (first generation Grubbs catalyst, 10 mol %) was added under Ar to a solution of amine **3a** (90 mg, 0.19 mmol) in anhydrous CH_2Cl_2 (5 mL) and the resulting mixture was heated at reflux overnight. The reaction mixture was filtered and concentrated. Flash chromatography of the crude residue (1:1 hexanes–AcOEt) gave **4a**: 50 mg (60%); ^{1}H NMR (1:1 mixture of rotamers) δ 1.25 and 1.44 (2s, 9H), 3.82 (m, 2H), 3.88 and 4.02 (2br s, 2H), 4.55 and 4.68 (2s, 2H), 5.60 and 5.71 (2m, 1H), 5.85 (m, 1H), 7.22–7.53 (m, 7H), 7.73 (m, 1H), 8.20 (m, 1H); ^{13}C NMR δ 23.4 (CH_2), 28.3 (3CH_3), 42.6 (CH_2), 45.9 and 46.5 (CH_2), 79.9 (C), 114.8 (CH), 117.8 (CH), 118.6 (C), 123.3 (CH), 124.2 (CH), 126.2 (2CH), 127.1 (CH), 128.2 (CH), 129.0 (C), 129.1 (2CH), 133.5 (CH), 136.0 (2C), 139.0 (C), 155.0 (CO). Anal. Calcd for $C_{24}H_{26}N_2O_4S\cdot 1/2H_2O$: C, 64.36%; H, 6.08%; N, 6.25%. Found: C, 64.36%; H, 5.94%; N, 6.12%.

4.1.5. 7-(Phenylsulfonyl)-2-tosyl-1,2,3,6-tetrahydroazocino[4,3-*b*]indole (4b). Operating as above, from amine **3b** (0.1 g, 0.19 mmol) **4b** was obtained: 80 mg (89%); ^{1}H NMR (^{1}H COSY) δ 2.40 (s, 3H, Me), 3.76 (d, J=6.6 Hz, 2H, 3-H), 3.98 (d, J=6.9 Hz, 2H, 6-H), 4.51 (s, 2H, 1-H), 5.42 (m, 1H, 4-H), 5.92 (m, 1H, 5-H), 7.20–7.70 (m, 12H, Ar), 8.20 (d, J=7.5 Hz, 1H, 8-H); ^{13}C NMR (Hetcor) δ 21.5 (CH_3), 25.0 (C-6), 42.1 (C-1), 45.0 (C-3), 114.8 (C-8), 115.3 (C-11b), 117.9 (C-11), 123.6 (C-10), 124.6 (C-9), 125.2 (C-4), 126.1 (2CH), 127.0 (2CH), 129.0 (C-11a), 129.2 (2CH), 129.6 (2CH), 129.8 (C-5), 133.7 (CH), 136.0 (2C), 136.4 (C), 138.8 (C), 143.3 (C); HRMS calcd for $C_{26}H_{24}N_2O_4S_2$ 492.6118, found 492.6110.

4.1.6. 2-[1-(*tert*-Butyldimethylsilyloxy)-2-propenyl]-1-(phenylsulfonyl)indole (6). $BrMgCH{=}CH_2$ (1 M solution in THF, 2.96 mmol) was added to a solution of aldehyde **5**[12] (0.65 g, 2.28 mmol) in THF (15 mL) at −78 °C and the resulting mixture was stirred at rt overnight. The reaction mixture was diluted with 10% aqueous NH_4Cl and extracted with Et_2O. The organic extracts were dried and concentrated and the residue was purified by flash chromatography (9:1 hexanes–AcOEt) to give 1-(phenylsulfonyl)-2-(1-hydroxy-2-propenyl)indole (0.57 g). This compound was dissolved in DMF (5 mL) and treated with TBDMSCl (0.40 g, 2.7 mmol) and imidazole (0.30 g, 4.5 mmol) at 55 °C overnight. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic extracts were dried and concentrated. Flash chromatography (95:5 hexanes–AcOEt) of the residue gave **6**: 0.61 g (63%); ^{1}H NMR δ −0.01 and 0.10 (2s, 6H), 0.95 (s, 9H), 5.15 (d, J=10.0 Hz, 1H), 5.40 (d, J=15 Hz, 1H), 5.90 (br s, 1H), 6.20 (m, 1H), 6.85 (s, 1H), 7.25–7.50 (m, 6H), 7.60 (m, 2H), 8.15 (d, J=7.5 Hz, 1H); ^{13}C NMR δ −4.93 and −4.78 (2CH_3), 18.3 (C), 25.8 (3CH_3), 69.5 (CH), 109.8 (CH), 114.5 (CH_2), 115.0 (CH), 120.8 (CH), 123.8 (CH), 124.3 (CH), 126.3 (2CH), 129.0 (2CH), 129.9 (C), 133.6 (CH), 137.7 (C), 138.6 (C), 139.8 (CH), 144.4 (C); HRMS calcd for $C_{23}H_{29}NO_3SSi$ 427.1637, found 427.1640.

4.1.7. 1-(Phenylsulfonyl)-3-(tosylaminomethyl)indole (8). A solution of aldehyde **7**[13] (0.5 g, 1.75 mmol) and tosylamine (0.9 g, 5.25 mmol) in dry toluene (15 mL) was heated at reflux (Dean–Stark) for 24 h. The solvent was removed and the residue was dissolved in MeOH (10 mL) and treated with $NaBH_4$ (66 mg, 1.75 mmol) at rt for 24 h. The solvent was removed and the residue was diluted with H_2O and extracted with Et_2O. The organic extracts were dried and concentrated and the resulting residue was purified by flash chromatography (6:4 hexanes–AcOEt) to give tosylamine **8**: 0.54 g (70%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.41 (s, 3H), 4.22 (d, J=6.0 Hz, 1H), 5.04 (br s, 2H), 7.20–7.90 (m, 13H); ^{13}C NMR δ 21.5 (CH_3), 38.6 (CH_2), 113.4 (CH), 117.6 (C), 119.6 (CH), 123.3 (CH), 124.5 (CH), 125.0 (CH), 126.3 (2CH), 126.6 (2CH), 129.2 (2CH), 129.6 (2CH, C), 133.8 (CH), 136.1 (C), 137.8 (C), 138.9 (C), 143.4 (C); HRMS calcd for $C_{22}H_{20}N_2O_4S_2$ 440.0864, found 440.0857.

4.1.8. 3-[(*N*-Allyl-*N*-*tert*-butoxycarbonyl)aminomethyl]-1-(phenylsulfonyl)indole (9a). Allylamine (0.34 mL, 4.6 mmol), $NaBH(OAc)_3$ (1.46 g, 6.9 mmol), and AcOH (0.13 mL, 2.3 mmol) were successively added to aldehyde **7** (0.65 g, 2.3 mmol) in CH_2Cl_2 (15 mL) and the resulting mixture was stirred at rt overnight. The reaction mixture was diluted with H_2O, basified with 10% aqueous Na_2CO_3, and extracted with CH_2Cl_2. The organic extracts were dried and concentrated. Flash chromatography of the residue (98:2 CH_2Cl_2–MeOH) gave the secondary amine (0.5 g). This compound was dissolved in MeOH (16 mL) and treated with (t-BuOCO)$_2$O (0.57 g, 2.65 mmol) and Et_3N (7.4 mL, 5.3 mmol). After the mixture was heated at reflux for 4 h, the solvent was removed and the residue was diluted with CH_2Cl_2 and washed with 1 N HCl and brine. The organic extracts were dried and concentrated and the resulting residue was chromatographed (flash, 95:5 hexanes–AcOEt) to give **9a**: 0.66 g (68%); ^{1}H NMR δ 1.48 (s, 9H), 3.70 (br s, 2H), 4.52 (br s, 2H), 5.10 (m, 2H), 5.65 (m, 1H), 7.20–7.65 (m, 7H), 7.85 (m, 2H), 8.05 (d, J=7.5 Hz, 1H); ^{13}C NMR δ 28.3 (3CH_3), 40.8 (CH_2), 48.0 (CH_2), 79.9 (C), 113.5 (CH), 116.3 (CH_2), 119.6 (CH), 120.3 (CH), 123.2 (CH), 124.6 (CH), 124.8 (CH), 126.5 (2CH), 128.8 (C), 129.1 (2CH), 133.4 (CH), 133.7 (CH), 135.3 (C), 137.9 (C), 155.3 (CO); HRMS calcd for $C_{23}H_{26}N_2O_4S$ 426.1613, found 426.1610.

4.1.9. 3-[(*N*-Allyl-*N*-tosyl)aminomethyl]-1-(phenylsulfonyl)indole (9b). Aldehyde **7** (0.65 g, 2.3 mmol) was allowed to react as above with allylamine and the resulting secondary amine was dissolved in CH_2Cl_2 (12 mL) and treated with tosyl chloride (0.33 g, 1.75 mmol) and Et_3N (0.25 mL, 1.75 mmol) at rt overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with 1 N HCl and brine prior to drying and solvent evaporation. The resulting residue was purified by flash chromatography (1:1 hexanes–CH_2Cl_2) to give **9b**: 0.74 g (67%); mp 108 °C (Et_2O); ^{1}H NMR δ 2.44 (s, 3H), 3.70 (d, J=6.3 Hz, 2H), 4.43 (s, 2H), 4.90 (m, 2H), 5.37 (m, 1H), 7.25–7.95 (m, 13H), 8.01 (d, J=7.5 Hz, 1H); ^{13}C NMR δ 21.4 (CH_3), 41.8 (CH_2), 49.5 (CH_2), 113.3 (CH), 117.2 (C), 118.9 (CH_2), 120.1 (CH), 123.4 (CH), 125.0 (CH), 125.3 (CH), 126.4 (2CH), 126.9 (2CH), 129.1 (2CH), 129.5 (C), 129.6 (2CH), 131.9 (CH), 133.7 (CH), 135.1 (C), 136.7 (C), 137.7 (C), 143.4 (C). Anal. Calcd for $C_{25}H_{24}N_2O_4S_2$: C, 62.48%; H, 5.03%; N, 5.82%. Found: C, 62.58%; H, 5.21%; N, 5.69%.

4.1.10. 3-[(*N*-Allyl-*N*-*tert*-butoxycarbonyl)aminomethyl]-1-(methoxymethyl)indole (11a). Aldehyde **10**[14] (1.75 g, 9.2 mmol) in CH_2Cl_2 (30 mL) was allowed to react with allylamine (1.41 mL, 18.8 mmol) and then with (t-BuOCO)$_2$O (3.67 g, 16.8 mmol) as described in Section 4.1.8. After work-up and flash chromatography (7:3 hexanes–AcOEt), **11a** was obtained: 2.20 g (72%); ^{1}H NMR (50 °C) δ 1.50 (s, 9H), 3.21 (s, 3H), 3.74 (br s, 2H), 4.59 (s, 2H), 5.10 (m, 2H), 5.47 (s, 2H), 5.73 (m, 1H), 7.08 (s, 1H), 7.10–7.30 (m, 2H), 7.46 (d, J=8.0 Hz, 1H), 7.69 (d, J=7.5 Hz, 1H); ^{13}C NMR (50 °C) δ 28.5 (3CH_3), 40.6 (CH_2), 47.9 (CH_2), 55.8 (CH_3), 77.3 (CH_2), 79.6 (C), 109.8 (CH), 113.0 (C), 116.0 (CH_2), 119.6 (CH), 120.1 (CH), 122.4 (CH), 127.1 (CH), 128.2 (C), 134.1 (CH), 136.9 (C), 155.4 (CO). Anal. Calcd for $C_{19}H_{26}N_2O_3\cdot 1/4H_2O$: C, 68.14%; H, 7.97%; N, 8.36%. Found: C, 68.30%; H, 8.07%; N, 8.26%.

4.1.11. 3-[(*N*-Allyl-*N*-*tert*-butoxycarbonyl)aminomethyl]-2-(1-hydroxy-2-propenyl)-1-(methoxymethyl)indole (12). *tert*-BuLi (1.7 M in pentane, 0.87 mmol) was slowly added under Ar to a solution of indole **11a** (0.22 g, 0.72 mmol) in anhydrous THF (10 mL) at −78 °C, and the resulting solution was stirred for 2 h at −78 °C. Then, acrolein (0.11 mL, 1.8 mmol) was added and the mixture was stirred at −78 °C for 3.5 h. The reaction mixture was poured into 10% aqueous NH_4Cl and extracted with Et_2O. The organic extracts were dried and concentrated and the residue was purified by flash chromatography (8:2 hexanes–AcOEt) to give alcohol **12**: 0.22 g (79%, unstable oil); ^{1}H NMR (gHSQC,) δ 1.49 (s, 9H, 3CH_3), 3.26 (s, 3H, OMe), 3.75 (m, 2H, $NCH_2CH{=}$), 4.68 and 4.73 (2d, J=15.3 Hz, 2H, indCH_2N), 5.09 (m, 1H, $CH_2{=}$), 5.13 (m, 1H, $CH_2{=}$), 5.24 (dm, J=10.8 Hz, 1H, $CH_2{=}$), 5.35 (dm, J=17.0 Hz, 1H, $CH_2{=}$), 5.47 and 5.62 (2d, J=10.8 Hz, 2H, CH_2OMe), 5.72 (m, 2H, CHOH, CH=), 6.15 (m, 1H, CH=), 7.15 (m, 1H, ind 5-H), 7.24 (m, 1H, ind 6-H), 7.41 (d, J=8.1 Hz, 1H, ind 7-H), 7.68 (dm, J=8.1 Hz, 1H, ind 4-H); ^{13}C NMR δ 28.5 ($3CH_3$), 39.3 (CH_2), 47.9 (CH_2), 55.8 (CH_3), 66.6 (CH), 74.5 (CH_2), 80.0 (C), 109.5 (CH), 111.6 (C), 115.1 (CH_2), 115.9 (CH_2), 119.5 (CH), 120.5 (CH), 122.8 (CH), 128.0 (C), 134.0 (CH), 137.6 (C), 137.9 (C), 139.0 (CH), 155.7 (CO).

4.1.12. 3-[(*N*-Allyl-*N*-*tert*-butoxycarbonyl)aminomethyl]-2-[1-(*tert*-butyldimethylsilyloxy)-2-propenyl]-1-(methoxymethyl)indole (13). A solution of alcohol **12** (0.21 g, 0.5 mmol), TBDMSCl (0.25 g, 1.6 mmol), and imidazole (0.15 g, 2.1 mmol) in DMF (3 mL) was heated under Ar at 55 °C overnight. The reaction mixture was partitioned between 10% aqueous Na_2CO_3 and Et_2O and extracted with Et_2O. The organic extracts were dried and concentrated. Flash chromatography (9:1 hexanes–AcOEt) of the residue gave **13**: 0.18 g (64%); IR (film) 1690; ^{1}H NMR δ 0.19 (s, 6H), 0.93 (s, 9H), 1.55 (s, 9H), 3.32 (s, 3H), 3.60 (br s, 2H), 4.77 (br s, 2H), 5.14 (m, 2H), 5.20 (dm, J=9.0 Hz, 1H), 5.40 (d, J=15.0 Hz, 1H), 5.54 and 5.76 (2d, J=10.0 Hz, 2H), 5.77 (m, 2H), 6.20 (m, 1H), 7.18 (m, 1H), 7.27 (m, 1H), 7.52 (d, J=7.8 Hz, 1H), 7.68 (d, J=7.8 Hz, 1H); ^{13}C NMR δ −4.6 ($2CH_3$), 18.6 (C), 26.1 ($3CH_3$), 28.8 ($3CH_3$), 38.7 (CH_2), 47.3 (CH_2), 56.0 (CH_3), 68.1 (CH), 75.8 (CH_2), 80.0 (C), 109.9 (C), 110.8 (CH), 114.6 (CH_2), 116.0 (CH_2), 119.5 (CH), 120.6 (CH), 122.8 (CH), 128.4 (C), 134.1 (CH), 137.6 (CH), 138.3 (C), 139.9 (C), 155.8 (CO); HRMS calcd for $C_{28}H_{44}N_2O_4Si$ 500.3070, found 500.3062.

4.1.13. 3-[(*N*-Allyl-*N*-*tert*-butoxycarbonyl)aminomethyl]-1-(methoxymethyl)-2-propenoylindole (14). Alcohol **12** (39 mg, 0.1 mmol) and MnO_2 (87 mg, 1.0 mmol) in CH_2Cl_2 (6 mL) were stirred at rt for 60 h. The reaction mixture was filtered through Celite and the filtrate was concentrated. The resulting residue was purified by flash chromatography (8:2 hexanes–AcOEt) to give ketone **14**: 25 mg (64%); ^{1}H NMR δ 1.50 (s, 9H), 3.19 (s, 3H), 3.55 (br s, 2H), 4.86 (s, 2H), 4.90 (dm, J=15.0 Hz, 1H), 5.05 (dm, J=9.6 Hz, 1H), 5.60 (br s, 1H), 5.64 (s, 2H), 5.99 (dd, J=10.5, 1.5 Hz, 1H), 6.30 (dd, J=17.1, 1.5 Hz, 1H), 6.89 (dd, J=17.1, 10.5 Hz, 1H), 7.22 (m, 1H), 7.40 (m, 1H), 7.50 (d, J=7.8 Hz, 1H), 7.80 (br d, J=7.8 Hz, 1H); ^{13}C NMR δ 28.7 ($3CH_3$), 40.0 (CH_2), 47.5 (CH_2), 56.3 (CH_3), 75.4 (CH_2), 80.0 (C), 111.1 (CH), 116.6 (CH_2), 119.4 (C), 121.8 (CH), 122.2 (CH), 126.2 (CH), 127.3 (C), 131.2 (CH_2), 133.8 (CH), 135.2 (C), 137.3 (CH), 138.9 (C), 155.8 (CO), 187.7 (CO); HRMS calcd for $C_{22}H_{28}N_2O_4$ 384.2049, found 384.2033.

4.1.14. 2-(*tert*-Butoxycarbonyl)-6-(*tert*-butyldimethylsilyloxy)-7-(methoxymethyl)-1,2,3,6-tetrahydroazocino[4,3-*b*]indole (15). Diene **13** (0.17 g, 0.33 mmol) was allowed to react with $(PCy_3)_2(Cl)_2Ru$=CHPh (10 mol %) in CH_2Cl_2 (9 mL) as described in Section 4.1.4. After work-up and flash chromatography (95:5 hexanes–AcOEt), compound **15** was obtained: 0.135 g (85%); ^{1}H NMR (400 MHz, gHSQC, 1:1 mixture of rotamers) δ 0.07 (s, 6H, CH_3), 0.91 (s, 9H, CH_3), 1.46 and 1.49 (2s, 9H, CH_3), 3.18 (s, 3H, OCH_3), 3.50, 3.75, and 3.96 (3m, 2H, 3-H), 4.52, 4.68, 4.87, and 5.10 (4d, J=16.0 Hz, 2H, 1-H), 5.45 and 5.63 (2m, 1H, 5-H), 5.63 and 5.83 (2m, 2H, OCH_2), 5.91 and 6.03 (2m, 1H, 4-H), 6.18 (br s, 1H, 6-H), 7.16 (t, J=8.0 Hz, 1H, 10-H), 7.21 (t, J=8.0 Hz, 1H, 9-H), 7.45 (d, J=8.0 Hz, 1H, 8-H), 7.57 (d, J=8.0 Hz, 1H, 11-H); ^{13}C NMR (100.6 MHz, gHSQC, 1:1 mixture of rotamers) δ −4.6 ($2CH_3$), 18.4 (C), 26.0 ($3CH_3$), 28.7 and 28.8 ($3CH_3$), 41.2 and 41.6 (C-1), 43.9 and 44.3 (C-3), 55.9 (OCH_3), 66.4 and 66.5 (C-6), 75.2 and 75.4 (CH_2O), 79.8 and 80.2 (C), 109.5 and 109.6 (C), 110.2 and 110.3 (C-8), 118.4 and 118.5 (C-11), 120.3 and 120.4 (C-10), 122.3 and 122.4 (C-9), 126.1 and 126.5 (C-5), 127.8 and 127.9 (C), 136.1 and 136.3 (C-4), 136.9 (C), 137.3 (C), 155.3 and 155.4 (CO); HRMS calcd for $C_{26}H_{40}N_2O_4Si$ 472.2757, found 472.2750.

4.1.15. 2-(*tert*-Butoxycarbonyl)-7-(methoxymethyl)-6-oxo-1,2,3,6-tetrahydroazocino[4,3-*b*]indole (16). (Im)-$(PCy_3)(Cl)_2Ru$=CHPh (second generation Grubbs catalyst, 10 mol %) was added under Ar to a solution of ketone **14** (25 mg, 0.065 mmol) in CH_2Cl_2 (2 mL) and the resulting mixture was stirred at rt overnight. The reaction mixture was filtered, the filtrate was concentrated, and the resulting residue was purified by flash chromatography (8:2 hexanes–AcOEt) to give **16**: 20 mg (86%); ^{1}H NMR (400 MHz) δ 1.48 (br s, 9H), 3.27 (s, 3H), 3.91 (br s, 2H), 4.83 (s, 2H), 5.99 (s, 2H), 6.44 (m, 1H), 6.63 (d, J=11.7 Hz, 1H), 7.26 (m, 1H), 7.43 (m, 1H), 7.55 (d, J=8.4 Hz, 1H), 7.90 (m, 1H); ^{13}C NMR (100.6 MHz) δ 28.8 ($3CH_3$), 37.2 (CH_2), 39.6 (CH_2), 56.3 (CH_3), 75.4 (CH_2), 81.1 (C), 111.6 (CH), 121.4 (CH, C), 122.0 (CH), 126.5 (C), 127.6 (CH), 133.7 (C), 135.7 (CH), 138.4 (C), 139.9 (CH), 154.6 (CO), 184.2 (CO). Anal. Calcd for $C_{20}H_{24}N_2O_4 \cdot 1/2H_2O$: C, 65.74%; H, 6.90%; N, 7.67%. Found: C, 65.85%; H, 6.66%; N, 7.65%.

4.1.16. 2-(*tert*-Butoxycarbonyl)-6-(*tert*-butyldimethylsilyloxy)-7-(methoxymethyl)-1,2,3,4,5,6-hexahydroazocino[4,3-*b*]indole (17). Compound **15** (63 mg, 0.13 mmol) dissolved in MeOH (6 mL) was hydrogenated over Pd/C (5%, 3.5 mg) for 12 h. The catalyst was filtered, the filtrate was concentrated, and the resulting residue was purified by flash chromatography (8:2 hexanes–AcOEt) to give azocinoindole **17**: 51 mg (80%); ^{1}H NMR (400 MHz) δ 0.08 (s, 3H), 0.93 (s, 9H), 1.46 and 1.55 (2s, 9H), 1.8 (m, 2H), 2.15 (m, 1H), 2.90 (m, 1H), 3.23 (s, 3H), 3.50 and 3.85 (2m, 2H), 4.85 (m, 2H), 5.51 (m, 1H), 5.56 and 5.68 (2d, J=14.4 Hz, 2H), 7.10–7.26 (m, 2H), 7.42 (d, J=8.0 Hz, 1H), 7.75 (m, 1H); ^{13}C NMR (1:1 mixture of rotamers) δ −4.64 ($2CH_3$), 18.5 (C), 24.0 and 24.1 (CH_2), 26.2 ($3CH_3$), 29.0 ($3CH_3$), 36.9 and 37.3 (CH_2), 39.4 and 39.7 (CH_2), 43.9 and 44.2 (CH_2), 56.0 (CH_3), 67.4 (CH), 74.6 (CH_2), 79.9 (C), 109.5 and 109.7 (CH), 110.4 and 110.5 (C), 119.1 and 119.5 (CH), 120.3 and 120.5 (CH), 122.4 (CH), 127.99 and 128.5 (C), 137.5 (C), 139.5 (C), 155.4 (CO); HRMS calcd for $C_{26}H_{42}N_2O_4Si$ 474.7083, found 474.7078.

4.1.17. 2-(*tert*-Butoxycarbonyl)-6-oxo-7-(methoxymethyl)-1,2,3,4,5,6-hexahydroazocino[4,3-*b*]indole (18). Operating as above, from **16** (0.28 g, 0.78 mmol) azocinoindole **18** was obtained after flash chromatography (6:4 hexanes–AcOEt): 0.23 g (82%); ^{1}H NMR (1:1 mixture of rotamers) 1.19 and 1.45 (2s, 9H), 2.10 (br, 2H), 2.95 (br, 2H), 3.21 (s, 3H), 3.55 and 3.65 (2m, 2H), 4.80 and 4.90 (2br s, 2H), 5.73 (br, 2H), 7.20 (t, J=8.0 Hz, 1H), 7.38 (t, J=8.0 Hz, 1H), 7.50 (br d, J=8.0 Hz, 1H), 7.70 (m, 1H); ^{13}C NMR (1:1 mixture of rotamers) 25.3 and 25.6 (CH_2), 28.2 and 28.3 ($3CH_3$), 41.7 and 41.9 (CH_2), 43.4 and 44.1 (CH_2), 46.1 and 47.9 (CH_2), 55.8 (CH_3), 74.7 (CH_2), 80.0 (C), 110.7 and 110.9 (CH), 120.2 and 120.5 (CH), 121.3 and 121.4 (CH), 122.3 (C), 125.8 and 126.0 (CH, C), 132.5 (C), 137.8 (C), 155.4 (CO), 197.6 and 198.2 (CO); HRMS calcd for $C_{20}H_{26}N_2O_4$ 358.1892, found 358.1887.

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