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Sequential ring-closing metathesis–vinyl halide Heck cyclization reactions: access to the tetracyclic ring system of ervitsine

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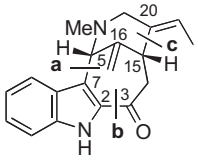
ABSTRACT

A chemoselective indole-templated ring-closing metathesis is used to assemble the cyclohepta[*b*]indole substructure of the indole alkaloid ervitsine. A subsequent intramolecular Heck coupling of the resulting alkene functionality with an amino-tethered vinyl halide accomplishes the closure of the unique 2-azabicyclo[4.3.1]decane framework of the alkaloid with concomitant incorporation of the exocyclic *E*-ethylidene substituent.

1. Introduction

Ervitsine[1] is a minor indole alkaloid isolated in 1977 from *Pandaca boiteaui* (Apocynaceae)[2] with an unique tetracyclic framework comprising a 2-azabicyclo[4.3.1]decane system fused to the indole ring and two exocyclic alkylidene (16-methylene and 20*E*-ethylidene) substituents. This complex architecture attracted the synthetic interest of research groups in the eighties and early nineties, resulting in a few approaches to the core structure[3,4] and a total synthesis based on biomimetic considerations.[5] Despite the variety of strategies used, all routes have in common the formation of the central carbocyclic ring in the last synthetic steps, either by cyclization of an iminium-type ion upon the indole 3-position (bond formed C_5–C_7, **a**)[3a,d,4,5] or by Friedel–Crafts acylation of the indole 2-position (bond formed C_2–C_3, **b**).[3b,c,e]



Ervitsine
(biogenetic numbering)

a refs 3a, 3d, 4,5
b refs 3b, 3c, 3e
c this work

Our long-standing interest in the development of indole annulation methodologies led us to envisage a straightforward synthetic approach to the bridged ervitsine framework relying on an indole-templated ring-closing metathesis (RCM)[6] to first construct the central seven-membered ring and a vinyl halide Heck cyclization[7] to close the piperidine ring and at the same time install the requisite 20*E*-ethylidene substituent (bond formed C_{15}–C_{20}, **c**).[8] As shown in Scheme 1, the metathetic ring closure of 2,3-dialkenylindoles of general structure **A** would provide cyclohepta[*b*]indoles **B**, with the appropriate double bond functionality for the subsequent intramolecular Heck reaction with the amino-tethered vinyl halide.[9] It should be noted that similar Heck couplings of vinyl halides and elaborated cyclohexenes[10] or cycloheptenes[11] have proved to be useful for the assembly of the bridged core of several indole alkaloids. In this context, we have successfully explored vinyl halide Heck reactions upon azocine and azonine rings for the total synthesis of apparicine[12] and cleavamines.[13]

2. Results and discussion

To explore the feasibility of the double annulation RCM–Heck methodology for the ervitsine construction, we initially focused on indolic precursors unfunctionalized at the benzylic α-position (Scheme 1, Y=H, H), knowing that this methylene group could be oxidized at a later stage of the synthesis.[14] Thus, cyclohepta[*b*]indoles **7**–**9** and **13** were selected as substrates for the key Heck reaction bearing different (carbamate, amine, and amide) exocyclic nitrogen atoms (Scheme 2). The synthetic route began with 2-allyl-3-indolecarbaldehyde **1**,[15] which was equipped with a strong electron-withdrawing group at the nitrogen to guarantee the stability of the gramine [3-(aminomethyl)indole] moiety of the

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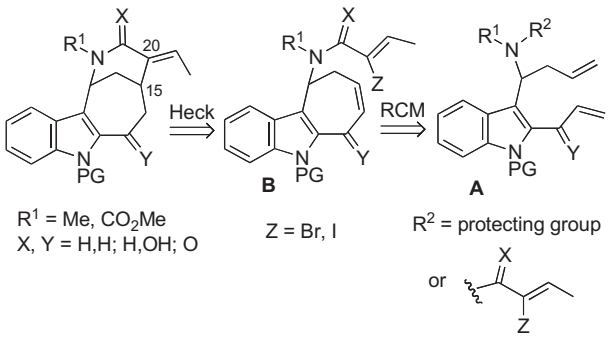
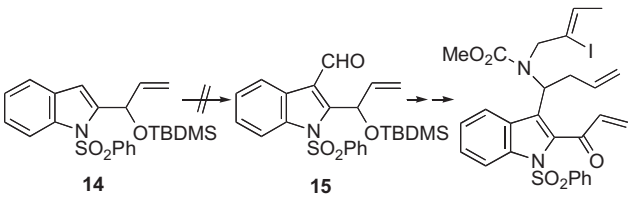


Scheme 1. Synthetic plan.

intermediates. From this compound, an amination–imine allylation sequence was devised to install the homoallylic amine moiety required for the RCM step. We chose a direct route without using protecting groups and incorporated the additional haloalkenyl appendage either at the amination step (for **7**–**9**) or at the final acylation step (for **13**), with the hope that it would be sufficiently inert under the RCM conditions. Reaction of aldehyde **1** with (*Z*)-2-bromo-2-butenylamine (**2a**), followed by alkylation of the resulting imine with allylmagnesium bromide led to the unstable secondary amine **3a** (not isolated), which was subsequently acylated with $ClCO_2Me$ or alkylated with formaldehyde and $NaCNBH_3$ to give carbamate **4** or tertiary amine **6** in 60% and 50% overall yield, respectively. Starting from **1** and (*Z*)-2-iodo-2-butenylamine (**2b**), carbamate **5** was similarly prepared in 65% overall yield through secondary amine **3b**. On the other hand, reaction of aldehyde **1** with methylamine and allylation of the resulting imine as above gave the unstable secondary amine **10**, which was converted into amide **12** in 60% overall yield by acylation with (*Z*)-2-bromo-2-butenoic acid (**11**) in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC).

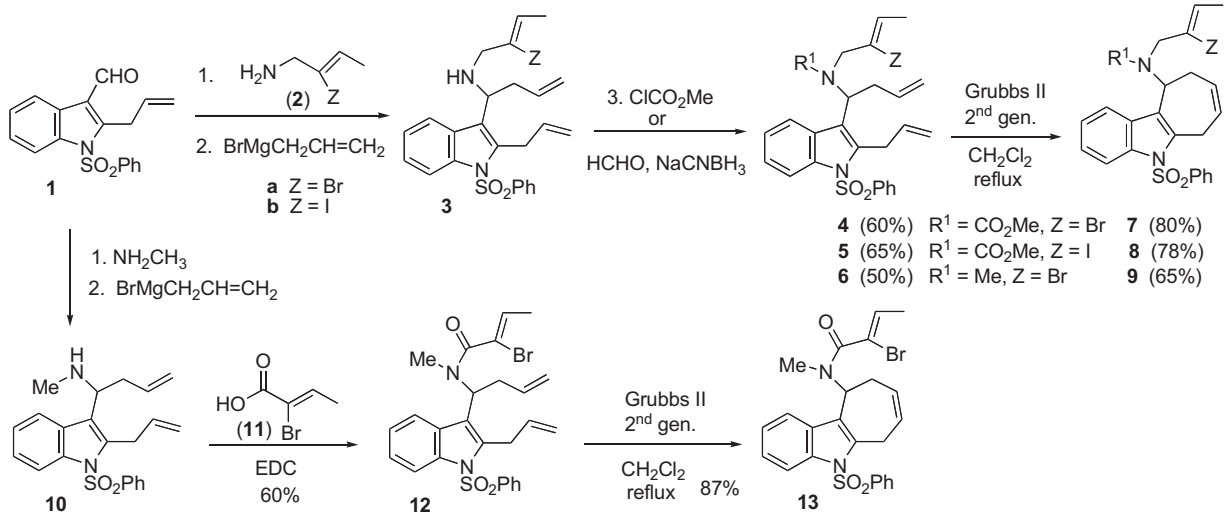
At this point we proceeded to study the RCM reaction. Considering the different substitution and electronic nature of the double bonds of the trienic substrates, we expected the preferred RCM event to be the indole-templated cyclization leading to a fused seven-membered ring. Our expectations were confirmed when carbamates **4** and **5** as well as amide **12**, on exposure to the second generation Grubbs catalyst in refluxing CH_2Cl_2, gave the desired cycloheptenes **7**, **8**, and **13** as the only products in 80%, 78%, and 87% yield, respectively. The tertiary amine **6** was a worse RCM substrate, requiring the previous conversion into the corresponding hydrochloride to afford **9** in a slightly lower yield (65%).

We also sought to elaborate functionalized tricyclic ervitsine substructures (**B**, Y=H, OH or O, Scheme 1) but all our efforts met with failure. The simple extension of the chemistry outlined above to an *O*-protected 2-(1-hydroxyallyl)indole such as **15**[15] (Scheme 3) proved impractical as the formyl group required for the amination–imine allylation step could not be introduced, only complex mixtures being obtained when **14** was subjected to the Friedel–Crafts protocol (Cl_2CHOMe, $TiCl_4$).



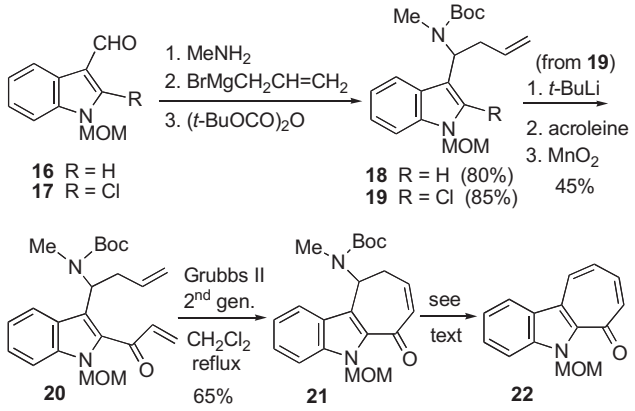
Scheme 3.

We then planned to install the homoallylic amine moiety on an indole-3-carbaldehyde such as **16**[16] or **17**[17] before functionalizing the 2-position either by direct metalation or metal–halogen exchange followed by electrophilic trapping (Scheme 4). Given that the base-sensitive halovinyl chain would probably be incompatible with the latter reaction, it would be introduced after the RCM step. Aldehyde **16** was uneventfully converted into carbamate **18** by successive treatment with methylamine, allylmagnesium bromide, and di-*tert*-butyl dicarbonate, but treatment of this substrate with LDA or alkyl lithium derivatives (*s*-BuLi, *t*-BuLi) in THF under a variety of experimental conditions, followed by addition of DMF, HCO_2Me, or acrolein, only led to the recovery of the starting material. More satisfactorily, the desired functionalization took place by lithium–halogen exchange from carbamate **19**, which was prepared as above from aldehyde **17**. Treatment with *t*-BuLi in THF at −78° C followed by quenching with acrolein led to an unstable alcohol, which was immediately oxidized with MnO_2 to give ketone **20** in 45% overall yield. Unfortunately, while RCM of **20** took place in the presence of the second generation Grubbs catalyst in refluxing CH_2Cl_2 to give the expected cyclopentenone **21** in 65% yield (not optimized), all attempts to remove the Boc protecting group for the



Scheme 2. Synthesis of cyclohepta[*b*]indoles **7**–**9** and **13**.

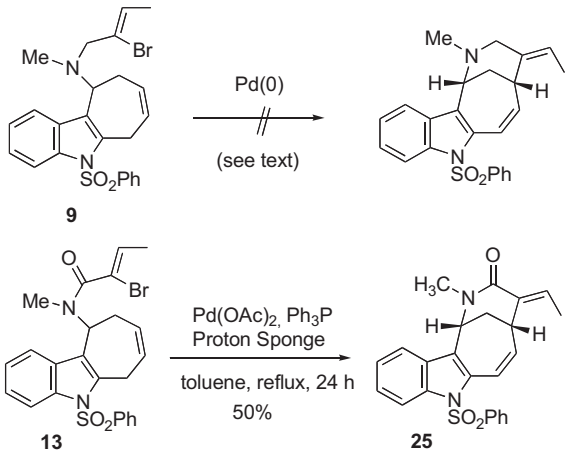
subsequent derivatization of the secondary amine invariably led to tropone **22**.



Scheme 4.

We turned our attention to the intramolecular Heck coupling to complete the bridged framework of ervitsine. Table 1 summarizes the survey of experimental conditions, including palladium pre-catalysts, ligands, and additives, using carbamates **7** and **8** as substrates. As can be observed in entry 1, only the starting product was recovered when vinyl bromide **7** was subjected to classical polar conditions[10a] ($Pd(OAc)_2$, PPh_3, Et_3N, CH_3CN). On the other hand, the use of ligand-free conditions introduced by Jeffery[18] ($Pd(OAc)_2$, K_2CO_3, TBACl, DMF, entry 2), which had proven successful for the synthesis of related azapolycyclic structures,[10b,c,e] resulted in the total decomposition of the material. More successfully, the desired cyclization proceeded upon treatment of **7** under non-polar conditions[11] (palladium catalyst, PPh_3, proton sponge, K_2CO_3, toluene, entries 3 and 4). However, although the conversion yields were good as evidenced by the NMR analysis of the crude reaction mixtures, the isolated yields of the (*E*)-ethylidene tetracycle **23** after column chromatography were only moderate (30%), the starting product being invariably recovered even under longer reaction times.

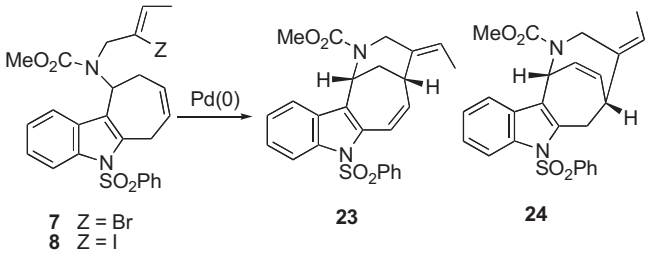
It should be mentioned that the analogous *N*-methyl derivative **9** (Scheme 5) led to complex reaction mixtures under any of the above Heck conditions. This result seemed to indicate that the presence of a basic nitrogen in the halobutene chain is not compatible with the harsh cyclization conditions, probably due to a competitive dealkylation process. So, unsurprisingly, amide **13** proved to be a more robust substrate leading to tetracyclic lactam **25** in 50% yield.



Scheme 5. Heck cyclization of **9** and **13**.

We then focused on the more reactive vinyl iodide **8**. When subjected to the same non-polar protocol (entry 5), tetracycle **23** was obtained only in a slightly better yield (45%) along with minor amounts of recovered starting product. To increase the efficiency of the process we examined the reaction in the presence of other additives, such as phenol or Ag_2CO_3. We were pleased to find that the addition of 20 mol % phenol in combination with K_3PO_4

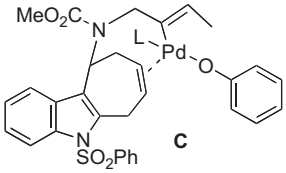
Table 1
Heck cyclization of cyclohepta[*b*]indoles **7** and **8**



Entry	Substrate	Reaction conditions	Products (yield %)[a]
1	**7**	$Pd(OAc)_2$ (16%), PPh_3 (50%), Et_3N (2 equiv), CH_3CN, reflux, 3 h	**7** (33)
2	**7**	$Pd(OAc)_2$ (5%), K_2CO_3 (5 equiv), TBACl (1 equiv), DMF, 60 °C, 4 h	––
3	**7**	$Pd(OAc)_2$ (5%), PPh_3 (20%), proton sponge (0.5 equiv), K_2CO_3 (1.1 equiv), toluene, reflux, 4 h	**23** (30) **7** (16)
4	**7**	$Pd(PPh_3)_4$ (5%), proton sponge (0.1 equiv), K_2CO_3 (2.5 equiv), toluene, sealed tube, 2.5 days	**23** (30) **7** (5)
5	**8**	$Pd(OAc)_2$ (10%), PPh_3 (40%), proton sponge (0.3 equiv), K_2CO_3 (1.5 equiv), toluene, reflux, 24 h	**23** (45) **8** (10)
6	**8**	$Pd(PPh_3)_4$ (10%), K_3PO_4 (3 equiv), Et_3N (6 equiv), phenol (0.2 equiv), toluene, reflux, 12 h	**23** (65)
7	**8**	$Pd(OAc)_2$ (10%), PPh_3 (30%), Ag_2CO_3 (3 equiv), toluene, reflux, 40 min	**23** (45) **24** (15)
8	**8**	$Pd(OAc)_2$ (10%), PPh_3 (30%), Ag_2CO_3 (3 equiv), toluene, 80 °C, 1 h	**23** (19) **24** (43)
9	**8**	$Pd(OAc)_2$ (10%), dppe (12%), Ag_2CO_3 (3 equiv), DIPEA (2 equiv), toluene, reflux, 2 h	**23** (25) **24** (25)

[a] Isolated yields after column chromatography.

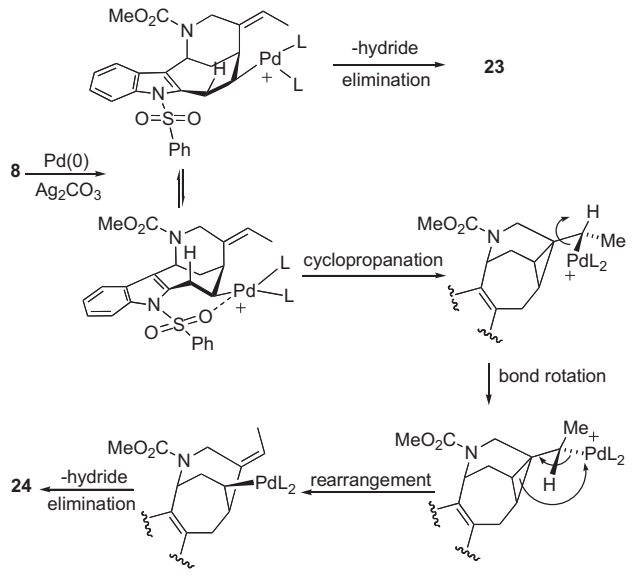
resulted in a cleaner cyclization, giving the ervitsine tetracycle **23** as the only product in 65% yield (entry 6). As far as we know, the use of phenol as a catalytic additive in the Heck reaction is unprecedented, although its positive role in some palladium-catalyzed arylations of ketone enolates has been previously observed.[19,20] According to these reports,[19] the intermediacy of a palladium phenoxide (e.g., **C**), which would stabilize an otherwise unstable intermediate, could account for the beneficial effect of the added phenol.



C

On the other hand, although the starting material was rapidly consumed in the presence of Ag_2CO_3 (entries 7–9), the cyclization followed a different course as it led to mixtures of tetracycles **23** and **24**, the latter coming from an apparent 7-*endo* cyclization with inversion of the ethylidene configuration.[21] Tetracycle **23** was the major product when the reaction was carried out in refluxing toluene (entry 7) while the formation of the abnormal product **24** was enhanced by working at lower temperatures (entry 8) or changing the ligand from Ph_3P to dppe (entry 9).

The formation of unusual Heck cyclization products like **24** has been previously observed[12b,22] and rationalized[23] by considering that the initial 6-*exo* cyclization is not followed by the expected β-hydride elimination (which would lead to **23**) but by an intramolecular carbopalladation on the exocyclic alkene. The resulting cyclopropane intermediate would undergo rearrangement, with concomitant inversion of the alkene geometry, and final β-hydride elimination. In our case, the competitive formation of **24** is only observed in the presence of Ag_2CO_3, probably because under these cationic conditions the benzenesulfonyl group is able to weakly coordinate with the initially formed cationic σ-alkyl palladium intermediate to give a seven-membered palladacycle[24] (Scheme 6). The β-hydride elimination would thus be partially prevented and the intramolecular cyclopropanation route favored, in particular when the reaction is performed at a relatively low temperature or in the presence of a chelating phosphine such as dppe.



Scheme 6.

3. Conclusions

We have succeeded in synthesizing tetracycles **23** and **25**, which embody the 4*E*-ethylidene-2-azabicyclo[4.3.1]decane bridged core of the indole alkaloid ervitsine, using a combination of an indole-templated RCM and a vinyl halide Heck cyclization. This result highlights the power of the double annulation RCM–Heck methodology for rapidly building up the highly complex structure present in some indole alkaloids.

4. Experimental section

4.1. General

All nonaqueous reactions were carried out under an argon atmosphere. All solvents were dried by standard methods. Reaction courses and product mixtures were routinely monitored by TLC on SiO_2 (silica gel 60 F_{254}) and the spots were located with aqueous potassium permanganate solution. Drying of organic extracts was carried out over anhydrous Na_2SO_4. The solvents were evaporated under reduced pressure with a rotary evaporator. Column chromatography was carried out using the flash chromatography technique on SiO_2 (silica gel 60, SDS, 0.04–0.06 mm). NMR spectra were recorded in $CDCl_3$ using Me_4Si as an internal reference. HRMS were obtained using an LC/MSD TOF mass spectrometer.

4.2. Synthesis of the RCM substrates

*4.2.1. (Z)-2-Bromo-2-butenylamine (**2a**).* (*Z*)-1,2-dibromo-2-butene[25] (3.12 g, 14.6 mmol) was added dropwise (1 h) to a solution of hexamethylenetetramine (2.25 g, 16 mmol) in $CHCl_3$ (18 mL) heated at reflux. The resulting mixture was heated at reflux for 4 h and then allowed to stand in the refrigerator overnight. The mixture was cooled in an ice bath and the quaternary salt was collected by filtration. The crude salt was dissolved in a warm solution, prepared from H_2O (6 mL), EtOH (29 mL), and 37% HCl (8 mL). The mixture was stirred for 4 h and then allowed to stand overnight. A precipitate of NH_4Cl was formed, which was removed by filtration, washing carefully with ethanol. The filtrate was concentrated to a quarter of the volume and the resulting solid was removed by filtration. The filtrate was concentrated to dryness and the solid residue was carefully dried. The residue was digested with MeOH (15 mL) and the resulting solid was removed by filtration. The filtrate was concentrated to dryness to give **2a** hydrochloride (2.75 g, quantitative), which was used in the next reaction without purification.

*4.2.2. 2-Allyl-3-[1-[N-(Z)-(2-bromo-2-butenyl)-N-(methoxycarbonyl)-amino]-3-butenyl]-1-(phenylsulfonyl)indole (**4**).* Et_3N (0.31 mL, 2.23 mmol) was added to a solution of amine **2a** hydrochloride (0.29 g, 1.5 mmol) in CH_2Cl_2 (5 mL) and the mixture was stirred at rt for 10 min. Aldehyde **1**[15] (0.34 g, 1.0 mmol) in CH_2Cl_2 (5 mL) and AcOH (0.06 mL, 1.0 mmol) were successively added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was diluted with CH_2Cl_2 (5 mL), basified with a saturated aqueous Na_2CO_3 solution (10 mL), and extracted with CH_2Cl_2 (2×10 mL). The organic extracts were dried and concentrated to give the crude imine (480 mg). Allylmagnesium bromide (1 M in Et_2O, 1.6 mL, 1.6 mmol) was added under Ar to a cooled (−78 °C) solution of the above imine in anhydrous THF (30 mL), and the resulting mixture was stirred at rt for 2 h. The reaction mixture was quenched with a 10% aqueous NH_4Cl solution (5 mL) and extracted with Et_2O (3×10 mL). The ethereal extracts were dried and concentrated to give the crude amine **3a** (342 mg). A solution of the above amine **3a** in anhydrous THF (12 mL) was added under Ar to a suspension of NaH (60%, 56 mg, 1.4 mmol) in THF (2 mL) cooled at −20 °C, and the mixture was stirred at −20 °C for 20 min. A solution of $ClCO_2Me$ (0.16 mL, 2.1 mmol) in THF (1 mL)

was then added and the mixture was stirred at rt overnight. The reaction mixture was quenched with H_2O (10 mL) and extracted with Et_2O (2×15 mL). The combined organic extracts were dried and concentrated. The resulting residue was chromatographed (97:3 hexanes/AcOEt) to give bromo triene **4** as a light brown oil: (0.35 g, 60%); ^{1}H NMR (400 MHz) δ 1.40 (d, J=6.4 Hz, 3H), 2.90 (m, 2H), 3.72 (s, 3H), 3.89 (m, 2H), 3.96 (br s, 2H), 4.95 (m, 2H), 5.03 (m, 2H), 5.41 (q, J=6.4 Hz, 1H), 5.56 (m, 1H), 5.60 (m, 1H), 5.96 (m, 1H), 7.26 (m, 2H), 7.41 (m, 2H), 7.53 (m, 1H), 7.66 (d, J=8.0 Hz, 1H), 7.73 (m, 2H), 8.21 (dm, J=8.0 Hz, 1H); ^{13}C NMR (74.5 MHz) δ 16.1 (CH_3), 30.2 (CH_2), 36.9 (CH_2), 51.4 (CH_2), 52.9 (CH_3), 53.2 (CH), 115.1 (CH), 116.3 (CH_2), 117.5 (CH_2), 118.8 (C), 120.1 (CH), 123.2 (CH), 123.6 (CH), 124.2 (CH), 124.3 (C), 126.4 (2CH), 129.2 (2CH), 129.4 (C), 133.7 (CH), 134.4 (CH), 134.8 (CH), 136.5 (C), 138.3 (C), 138.9 (C), 156.6 (CO); ESI-HRMS $[M+H]^+$ calcd for $C_{27}H_{30}BrN_2O_4S$ 557.1110, found 557.1104.

*4.2.3. 2-Allyl-3-[1-[N-(Z)-(2-iodo-2-butenyl)-N-(methoxycarbonyl) amino]-3-butenyl]-1-(phenylsulfonyl)indole (**5**).* Operating as above, from aldehyde **1**[15] (0.20 g, 0.6 mmol) and the amine **2b** hydrochloride[26] (0.25 g, 1.0 mmol), carbamate **5** was obtained as a light brown oil: 0.24 g (65%); ^{1}H NMR (400 MHz) δ 1.30 (d, J=6.4 Hz, 3H), 2.82 (m, 2H), 3.63 (s, 3H), 3.81 (m, 2H), 3.90 and 3.95 (2d, J=16 Hz, 2H), 4.82 (d, J=10.4 Hz, 1H), 4.90 (br s, 1H), 4.95 (m, 2H), 5.18 (q, J=6.4 Hz, 1H), 5.47 (m, 2H), 5.90 (m, 1H), 7.16 (m, 2H), 7.30 (m, 2H), 7.42 (m, 1H), 7.58 (dm, J=8 Hz, 1H), 7.65 (m, 2H), 8.12 (d, J=7.8 Hz, 1H); ^{13}C NMR (400 MHz) δ 21.3 (CH_3), 30.4 (CH_2), 36.7 (CH), 52.9 (CH_3), 53.2 (CH), 54.7 (CH_2), 105.5 (C), 115.0 (CH), 116.3 (CH_2), 117.6 (CH_2), 118.7 (C), 120.2 (CH), 123.7 (CH), 124.2 (CH), 126.4 (2CH), 129.0 (CH), 129.2 (2CH), 129.3 (C), 133.8 (CH), 134.4 (CH), 134.9 (CH), 136.4 (C), 138.2 (C), 138.9 (C), 156.6 (CO).

*4.2.4. 2-Allyl-3-[1-[N-(Z)-(2-bromo-2-butenyl)-N-methylamino]-3-butenyl]-1-(phenylsulfonyl)indole (**6**).* Aldehyde **1**[15] (0.17 g, 0.5 mmol) was allowed to react with **2a** hydrochloride and allylmagnesium bromide as described for the preparation of carbamate **4**. The resulting crude amine **3a** (170 mg) was dissolved in CH_3CN (1.5 mL) and the resulting solution was treated with 37% aqueous formaldehyde (1.7 mmol) and $NaBH_3CN$ (34 mg, 0.55 mmol) for 45 min at rt. The acidic pH was maintained with regular addition of AcOH. The reaction mixture was basified with 2 N NaOH (5 mL), diluted with H_2O (10 mL), and extracted with Et_2O (3×10 mL). The organic layer was washed with 2 N NaOH (2×10 mL), dried, and concentrated. The resulting residue was chromatographed (90:10 hexanes/AcOEt) to give **6** as a light brown oil: 134 mg (50%); ^{1}H NMR (400 MHz) δ 1.71 (d, J=6.4 Hz, 3H), 2.11 (s, 3H), 2.58 (m, 1H), 2.76 (m, 1H), 3.11 (br s, 2H), 3.54 (dd, J=9.6 and 4.8 Hz, 1H), 3.82 (m, 2H), 4.63 (d, J=9.6 Hz, 1H), 4.72 (d, J=18.4 Hz, 1H), 5.07 (m, 2H), 5.20 (m, 1H), 5.86 (q, J=6.4 Hz, 1H), 5.99 (m, 1H), 7.20 (m, 1H), 7.24 (m, 1H), 7.32 (m, 2H), 7.46 (m, 1H), 7.61 (m, 2H), 7.91 (d, J=7.6 Hz, 1H), 8.17 (d, J=8.4 Hz, 1H); ^{13}C NMR (74.5 MHz) δ 16.6 (CH_3), 30.6 (CH_2), 37.0 (CH_2), 39.6 (CH_3), 61.7 (CH), 63.8 (CH_2), 115.2 (CH), 116.4 (CH_2), 116.7 (CH_2), 121.7 (CH), 122.6 (C), 123.5 (CH), 124.4 (CH), 125.6 (CH), 126.2 (2CH), 126.8 (C), 128.9 (2CH), 129.4 (C), 133.4 (CH), 135.2 (CH), 135.3 (CH), 136.0 (C), 137.1 (C), 138.6 (C); ESI-HRMS $[M+H]^+$ calcd for $C_{26}H_{30}BrN_2O_2S$ 513.1205, found 513.1200.

*4.2.5. 2-Allyl-3-[1-(Z)-(2-bromo-N-methyl-2-butenamido)-3-butenyl]-1-(phenylsulfonyl)indole (**12**).* Methylamine (8 M in EtOH, 1.9 mL, 15 mmol) and AcOH (0.09 mL, 1.5 mmol) were successively added to a solution of aldehyde **1** (0.5 g, 1.5 mmol) in CH_2Cl_2 (15 mL). After being stirred at rt overnight, the reaction mixture was diluted with CH_2Cl_2 (10 mL), basified with a saturated Na_2CO_3 solution and extracted with CH_2Cl_2 (3×10 mL). The organic extracts were dried and concentrated to give the crude imine: 0.5 g. Allylmagnesium bromide (1 M in Et_2O, 2.4 mL, 2.4 mmol) was added under Ar to a cooled (−78 °C) solution of the above imine in anhydrous THF (30 mL), and the resulting mixture was stirred at rt overnight. The reaction mixture was quenched with a 10% aqueous NH_4Cl solution (10 mL) and extracted with Et_2O (3×15 mL). The ethereal extracts were dried and concentrated to give the crude amine **10** (0.5 g). Butenoic acid **11**[27] (0.49 g, 3 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC, 0.46 g, 3 mmol) were added to a solution of the above amine **10** in CH_2Cl_2 (30 mL) and the mixture was stirred at rt for 2.5 days. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with 1.5 M aqueous HCl (2×10 mL) and aqueous 10% NaOH (2×10 mL). The resulting organic solution was dried and concentrated and the resulting residue was chromatographed (95:5 hexanes/AcOEt) to give the title compound **12** as a pale yellow foam: 0.48 g (60%); ^{1}H NMR (400 MHz) δ 1.90 (d, J=6.6 Hz, 3H), 2.77 (s, 3H, NCH_3), 2.90 (m, 2H), 3.90 (m, 2H), 5.00 (m, 4H), 5.70 (m, 1H), 5.95 (m, 2H), 6.05 (q, J=6.6 Hz, 1H), 7.20 (m, 2H), 7.38 (m, 2H), 7.50 (m, 1H), 7.70 (m, 3H), 8.25 (d, J=8 Hz, 1H); ^{13}C NMR (74.5 MHz) δ 16.3 (CH_3), 30.1 (CH_2), 34.9 (CH_2), 32.3 (CH_3), 50.2 (CH), 115.5 (CH), 116.2 (CH_2), 117.6 (C), 117.7 (CH_2), 120.1 (CH), 123.8 (CH), 124.2 (CH), 126.3 (2CH), 127.0 (C), 129.1 (2CH), 129.3 (CH), 133.7 (CH), 134.0 (CH), 135.1 (CH), 135.2 (C), 136.8 (C), 138.5 (C), 138.9 (C), 166.3 (CO); ESI-HRMS $[M+H]^+$ calcd for $C_{26}H_{28}BrN_2O_3S$ 527.1004, found 527.0979.

4.3. RCM reactions

*4.3.1. 10-[N-((Z)-2-Bromo-2-butenyl)-N-(methoxycarbonyl)amino]-5-(phenylsulfonyl)-9,10-dihydro-6H-cyclohepta[b]indole (**7**).* The second generation Grubbs catalyst (7 mol %) was added under Ar to a solution of carbamate **4** (100 mg, 0.18 mmol) in CH_2Cl_2 (2.5 mL) and the resulting mixture was heated at reflux for 2.5 h. The reaction mixture was concentrated and the residue was chromatographed (96:4 hexanes/AcOEt) to give the title compound **7** as a yellow oil: 76 mg (80%); ^{1}H NMR (400 MHz) δ 1.49 (dm, J=6.5 Hz, 3H), 2.55 (br, 1H), 2.65 (br, 1H), 3.40 (d, J=16.8 Hz, 1H), 3.78 (br s, 3H), 4.05 (m, 3H), 5.36 (q, J=6.5 Hz, 1H), 5.75 (m, 1H), 5.88 (m, 1H), 5.95 (m, 1H), 7.26 (m, 3H), 7.43 (m, 2H), 7.53 (m, 1H), 7.70 (m, 2H), 8.23 (d, J=8.0 Hz, 1H); ^{13}C NMR (74.5 MHz) δ 16.3 (CH_3), 25.5 (br, CH_2), 30.4 (br, CH_2), 51.4 (br, CH), 51.9 (br, CH_2), 53.0 (br, CH_3), 115.3 (CH), 118.7 (br, CH), 120.0 (C), 123.0 (br, CH), 124.1 (CH), 124.8 (CH), 124.9 (C), 125.0 (C), 126.1 (2CH), 128.9 (CH), 129.3 (2CH), 130.3 (CH), 133.8 (CH), 136.1 (C), 137.2 (br, C), 138.7 (C), 156.7 (br, CO); ESI-HRMS $[M+Na]^+$ calcd for $C_{25}H_{25}BrN_2NaO_4S$ 551.0616, found 551.0591.

*4.3.2. 10-[N-((Z)-2-Iodo-2-butenyl)-N-(methoxycarbonyl)amino]-5-(phenylsulfonyl)-9,10-dihydro-6H-cyclohepta[b]indole (**8**).* Operating as above, from carbamate **5** (0.30 g, 0.5 mmol), the title compound **8** was obtained as a yellow oil after column chromatography (96:4 hexanes/AcOEt): 0.22 g (78%); ^{1}H NMR (400 MHz, major rotamer) δ 1.51 (d, J=6.0 Hz, 3H), 2.59 (br, 1H), 2.74 (br, 1H), 3.49 (d, J=16 Hz, 1H), 3.71 (d, J=16 Hz, 1H), 3.78 (br s, 3H), 3.99 (m, 2H), 5.25 (q, J=6 Hz, 1H), 5.72 (m, 1H), 5.86 (m, 1H), 5.95 (m, 1H), 7.22 (m, 1H), 7.29 (m, 2H), 7.44 (m, 2H), 7.54 (m, 1H), 7.71 (m, 2H), 8.23 (d, J=8.4 Hz, 1H); ^{13}C NMR (74.5 MHz) δ 21.6 (CH_3), 25.6 (br, CH_2), 30.9 (br, CH_2), 52.4 (br, CH), 53.1 (br, CH_3), 55.1 (br, CH_2), 106.9 (br, C), 115.2 (CH), 118.6 (br, CH), 119.7 (br, C), 124.1 (CH), 124.8 (CH), 126.1 (2CH), 126.4 (C), 128.9 (CH), 129.0 (CH), 129.4 (2CH), 130.2 (CH); 133.9 (CH), 136.1 (C), 137.2 (br, C), 138.8 (C), 156.9 (CO); ESI-HRMS $[M+Na]^+$ calcd for $C_{25}H_{25}IN_2NaO_4S$ 599.0472, found 599.0474.

*4.3.3. 10-[N-((Z)-2-Bromo-2-butenyl)-N-methylamino]-5-(phenylsulfonyl)-9,10-dihydro-6H-cyclohepta[b]indole (**9**).* Amine **6** hydrochloride (84 mg, 0.16 mmol) in CH_2Cl_2 (2.4 mL, 0.07 M) was heated at reflux in the presence of the second generation Grubbs catalyst (7 mol %) for 2 h. The reaction mixture was diluted with a saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried and

concentrated, and the resulting residue was chromatographed (97:3 hexanes/AcOEt) to give the title compound **9** as a light brown oil: 52 mg (65%); ^{1}H NMR (400 MHz) δ 1.70 (d, J=6 Hz, 3H), 2.03 (s, 3H), 2.40 (m, 1H), 2.60 (m, 1H), 3.12 and 3.22 (2d, J=14.0 Hz, 2H), 3.95 (m, 3H), 5.84 (m, 3H), 7.23 (m, 2H), 7.33 (m, 2H), 7.46 (m, 1H), 7.62 (m, 2H), 7.82 (d, J=7.5 Hz, 1H), 8.17 (d, J=8.0 Hz, 1H); ^{13}C NMR (74.5 MHz) δ 16.6 (CH_3), 25.3 (CH_2), 25.9 (CH_2), 36.9 (CH_3), 58.5 (CH), 63.2 (CH_2), 115.4 (CH), 120.8 (CH), 123.6 (CH), 124.1 (C), 124.3 (CH), 125.5 (CH), 126.1 (2CH), 126.9 (C), 128.6 (CH), 128.7 (CH), 128.9 (2CH), 131.4 (C), 133.5 (CH), 136.5 (C), 136.6 (C), 138.2 (C); ESI-HRMS $[M+H]^+$ calcd for $C_{24}H_{26}BrN_2O_2S$ 485.0892, found 485.0873.

*4.3.4. 10-((Z)-2-Bromo-N-methyl-2-butenamido)-5-(phenylsulfonyl)-9,10-dihydro-6H-cyclohepta[b]indole (**13**).* The second generation Grubbs catalyst (7 mol %) was added under Ar to a solution of amide **12** (50 mg, 0.09 mmol) in CH_2Cl_2 (2 mL) and the resulting mixture was heated at reflux for 3 h. The reaction mixture was concentrated and the residue was chromatographed (95:5 hexanes/AcOEt) to give the title compound **13** as a light brown foam: 41 mg (87%); ^{1}H NMR (400 MHz, major rotamer) δ 1.82 (d, J=6.8 Hz, 3H), 2.47 (s, 3H), 2.55 (m, 1H), 2.75 (m, 1H), 3.90 (m, 2H), 5.90 (br s, 1H), 5.99 (m, 2H), 6.20 (br q, J=6.8 Hz, 1H), 7.20–7.45 (m, 5H), 7.52 (m, 1H), 7.67 (d, J=7.2 Hz, 2H), 8.23 (d, J=8 Hz, 1H); ^{13}C NMR (74.5 MHz) δ 16.3 (CH_3), 25.1 (CH_2), 28.9 (CH_2), 32.9 (CH_3), 49.3 (CH), 115.6 (CH), 117.3 (C), 118.6 (CH), 124.4 (CH), 125.0 (CH), 126.1 (2CH), 129.1 (2CH), 129.2 (1CH), 130.2 (C), 130.7 (CH), 133.7 (CH), 136.5 (C), 137.2 (C), 138.5 (C), 166.6 (CO), one quaternary C not observed; ESI-HRMS $[M+H]^+$ calcd for $C_{24}H_{24}BrN_2O_3S$ 499.0691, found 499.0695.

4.4. Synthesis of cyclohepta[*b*]indole 21

*4.4.1. 3-[1-(N-tert-Butoxycarbonyl-N-methylamino)-3-butenyl]-1-(methoxymethyl)indole (**18**).* Methylamine (8 M in EtOH, 1.32 mL, 10.6 mmol) and AcOH (0.06 mL, 1.06 mmol) were successively added to a solution of aldehyde **16**[16] (0.2 g, 1.06 mmol) in CH_2Cl_2 (8 mL). After being stirred at rt overnight, the reaction mixture was diluted with CH_2Cl_2 (5 mL), basified with a saturated Na_2CO_3 solution, and extracted with CH_2Cl_2 (3×10 mL). The organic extracts were dried and concentrated to give the crude imine. Allylmagnesium bromide (1 M in Et_2O, 1.59 mL, 1.59 mmol) was added under Ar to a cooled (−78 °C) solution of the above material in anhydrous THF (25 mL), and the mixture was stirred at rt overnight. The reaction mixture was quenched with a 10% aqueous NH_4Cl solution (10 mL) and extracted with Et_2O (3×10 mL). The organic extracts were dried and concentrated to give the crude secondary amine. Et_3N (0.85 mL, 6.08 mmol) and $(Boc)_2O$ (0.46 g, 2.12 mmol) were successively added to a solution of the above material in MeOH (30 mL) and the mixture was heated at reflux for 5 h. The solvent was removed and the residue was diluted with CH_2Cl_2 (30 mL) and washed with 1 N HCl (2×20 mL) and brine (2×20 mL). The organic solution was dried and concentrated and the residue was chromatographed (85:15 hexanes/AcOEt) to give carbamate **18** as a light brown foam: 0.29 g (80%); ^{1}H NMR (300 MHz, mixture of rotamers) δ 1.50 and 1.57 (2br s, 9H), 2.50 (br, 3H), 2.71 (m, 2H), 3.24 (s, 3H), 5.08 (br d, J=10.5 Hz, 1H), 5.17 (dm, J=17.1 Hz, 1H), 5.43 (s, 2H), 5.60 and 5.86 (2br m, 2H), 7.08 (s, 1H), 7.14 (td, J=7.5 and 1 Hz, 1H), 7.25 (td, J=7.5 and 1 Hz, 1H), 7.45 (d, J=7.5 Hz, 1H), 7.64 (br d, J=7.5 Hz, 1H); ^{13}C NMR (75.4 MHz, mixture of rotamers) δ 27.9 (CH_3), 28.5 (CH_3), 35.5 (CH_2), 49.9 and 51.5 (CH), 55.9 (CH_3), 77.3 (CH_2), 79.1 (C), 109.7 (CH), 115.9 (C), 116.8 and 117.1 (CH_2), 119.8 (CH), 120.3 (CH), 122.7 (CH), 126.0 (CH), 128.0 (C), 134.9 (CH), 136.9 (C), 155.9 (C).

*4.4.2. 3-[1-(N-tert-Butoxycarbonyl-N-methylamino)-3-butenyl]-2-chloro-1-(methoxymethyl)indole (**19**).* Operating as above, from aldehyde **17**[17] (0.3 g, 1.28 mmol) carbamate **19** was obtained as a light brown foam after chromatography (85:15 hexanes/AcOEt): 412 mg (85%); ^{1}H NMR (300 MHz) δ 1.51 (s, 9H), 2.69 (s, 3H), 2.82–3.08 (m, 2H), 3.28 (s, 3H), 5.04 (dm, J=9 Hz, 1H), 5.16 (dm, J=15 Hz, 1H), 5.53 (s, 2H), 5.72–5.90 (m, 2H), 7.19 (t, J=7.5 Hz, 1H), 7.24 (t, J=7.5 Hz, 1H), 7.42 (d, J=7.5 Hz, 1H), 7.74 (d, J=7.5 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 28.8 (CH_3), 29.2 (CH_3), 35.5 (CH_2), 52.1 (CH), 56.3 (CH_3), 74.1 (CH_2), 79.8 (C), 110.1 (CH), 111.2 (C), 117.4 (CH_2), 119.8 (CH), 121.4 (CH), 123.1 (CH), 124.9 (C), 127.5 (C), 135.4 (CH), 136.0 (C), 155.7 (C); ESI-HRMS $[M+Na]^+$ calcd for $C_{20}H_{27}ClN_2NaO_3$ 401.1602, found 401.1619.

*4.4.3. 3-[1-(N-tert-Butoxycarbonyl-N-methylamino)-3-butenyl]-1-(methoxymethyl)-2-(1-oxo-2-propenyl)indole (**20**).* *t*-BuLi (1.7 M in pentane, 0.6 mL, 1.02 mmol) was slowly added to a solution of 2-chloroindole **19** (254 mg, 0.67 mmol) in THF (12 mL) cooled at −78 °C and the resulting mixture was stirred at −78 °C for 30 min. Acrolein (0.13 mL, 1.92 mmol) was added and the mixture was stirred at −78 °C for 20 min. The reaction mixture was quenched with 10% aqueous NH_4Cl (15 mL) and extracted with Et_2O (3×15 mL). The organic extracts were dried and concentrated and the resulting residue was chromatographed (1:1 hexanes/AcOEt) to give the crude carbinol. A solution of the above material in CH_2Cl_2 (15 mL) was treated with MnO_2 (0.58 g, 6.7 mmol) at rt overnight. The reaction mixture was filtered through Celite and the filtrate was concentrated to give ketone **20** as a light brown foam: 120 mg (45%); ^{1}H NMR (300 MHz, major rotamer) δ 1.47 (s, 9H), 2.75 (s, 3H), 2.80 (m, 2H), 3.16 (s, 3H), 4.95 (dm, J=9 Hz, 1H), 5.15 (dm, J=15 Hz, 1H), 5.46 (d, J=8.8 Hz, 1H), 5.53 (d, J=8.8 Hz, 1H), 5.57 (m, 2H), 6.08 (d, J=9H, 1H), 6.18 (d, J=15 Hz, 1H), 6.81 (dd, J=15 and 8.8 Hz), 7.22 (t, J=7.5 Hz, 1H), 7.35 (t, J=7.5 Hz, 1H), 7.51 (d, J=7.5 Hz, 1H), 7.85 (d, J=7.5 Hz, 1H); ^{13}C NMR (75.4 MHz, major rotamer) δ 28.8 (CH_3), 29.8 (CH_3), 36.4 (CH_2), 52.3 (CH), 56.2 (CH_3), 75.4 (CH_2), 79.9 (C), 111.2 (CH), 117.6 (CH_2), 118.1 (C), 121.7 (CH), 122.4 (CH), 124.9 (CH), 127.2 (C), 132.3 (CH_2), 135.0 (CH), 135.4 (C), 138.0 (CH), 139.3 (C), 155.5 (C), 197.0 (C); ESI-HRMS $[M+Na]^+$ calcd for $C_{23}H_{30}N_2NaO_4$ 421.2097, found 421.2089.

*4.4.4. 10-(N-tert-Butoxycarbonyl-N-methylamino)-5-(methoxymethyl)-9,10-dihydro-5H-cyclohepta[b]indole-6-one (**21**).* The second generation Grubbs catalyst (30 mg, 7 mol %) was added under Ar to a solution of ketone **20** (0.2 g, 0.50 mmol) in CH_2Cl_2 (30 mL) and the resulting mixture was heated at reflux overnight. The reaction mixture was concentrated and the residue was chromatographed (9:1 hexanes/AcOEt) to give **21** as a pale yellow foam: 120 mg (65%); ^{1}H NMR (300 MHz, major rotamer) δ 1.54 (s, 9H), 2.66 (s, 3H), 2.85–3.05 (m, 2H), 3.32 (s, 3H), 6.01 (d, J=10.5 Hz, 1H), 6.10 (d, J=10.5 Hz, 1H), 6.32 (d, J=11 Hz, 1H), 6.65 (m, 1H), 7.18–7.30 (m, 2H), 7.44 (t, J=7.5 Hz, 1H), 7.56 (d, J=7.5 Hz, 1H), 7.71 (m, 1H); ^{13}C NMR (75.4 MHz, major rotamer) δ 28.8 (CH_3), 31.7 (CH_3), 33.3 (CH_2), 49.7 (CH), 56.4 (CH_3), 75.9 (CH_2O), 80.1 (C), 111.5 (CH), 121.9 (CH), 122.2 (CH), 123.6 (C), 126.4 (C), 127.6 (CH), 134.8 (CH), 139.4 (CH), 140.2 (C), 155.5 (C), 185.4 (C). One quaternary C was not observed; ESI-HRMS calcd for $C_{21}H_{26}N_2O_4$ 370.1892, found 370.1910.

*4.4.5. 5-(Methoxymethyl)cyclohepta[b]indol-6-one (**22**).* Yellow amorphous solid. ^{1}H NMR (400 MHz) δ 3.37 (s, 3H), 6.52 (s, 2H), 7.01 (m, 1H), 7.24–7.38 (m, 2H), 7.42 (tm, J=8 Hz, 1H), 7.62 (tm, J=8 Hz, 1H), 7.75 (d, J=8 Hz, 1H), 8.12 (m, 2H); ^{13}C NMR (100.5 MHz) δ 56.2 (CH_3), 75.6 (CH_2), 112.2 (CH), 120.8 (CH), 122.7 (CH), 124.9 (CH), 125.1 (C), 126.0 (C), 128.4 (CH), 129.3 (CH), 135.3 (CH), 138.0 (CH), 140.3 (C), 140.5 (C), 179.7 (C); ESI-HRMS calcd for $C_{15}H_{13}NO_2$ 239.0946, found 239.0944.

4.5. Heck cyclizations

*4.5.1. 4-(E)-Ethylidene-2-(methoxycarbonyl)-8-(phenylsulfonyl)-2,3,4,5-tetrahydro-1,5-methano-1H-azonino[4,3-b]indole (**23**).* $Pd(PPh_3)_4$ (17 mg, 0.015 mmol), K_3PO_4 (96 mg, 0.45 mmol),

phenol (3.5 mg, 0.04 mmol), and Et_3N (0.1 mL, 0.75 mmol) were successively added to a solution of vinyl iodide **8** (87 mg, 0.15 mmol) in toluene (11 mL), and the resulting mixture was heated at reflux for 12 h. The reaction mixture was diluted with Et_2O and washed with a saturated aqueous Na_2CO_3 solution and brine. The organic layer was dried and concentrated. The resulting residue was chromatographed (hexanes and 95:5 hexanes/EtOAc) to give the title compound **23** as a light brown oil: 43 mg (65%); ^{1}H NMR (400 MHz, assignment aided by gHSQC, 2:1 mixture of rotamers) δ 1.70 (dm, J=6.4 Hz, 3H), 1.91 (d, J=13 Hz, 1H, 13-H), 2.25 (m, 1H, 13-H), 2.94 and 3.10 (major) (2d, J=13.5 Hz, 1H, 3-H), 3.67 (major) and 3.81 (2s, 3H, OCH_3), 3.81 (masked, 1H, 5-H), 4.04 (major) and 4.17 (d, J=13.5 Hz, 1H, 3-H), 5.37 (major) and 5.42 (2q, J=6.4 Hz, 1H), 5.73 and 5.91 (major) (2 br s, 1H, 1-H), 6.05 (m, 1H), 7.31 (m, 1H), 7.34 (m, 1H), 7.36 (m, 2H), 7.49 (m, 2H), 7.67 (m, 2H), 7.85 (d, J=8 Hz, 1H), 8.25 (d, J=8 Hz, 1H); ^{13}C NMR (74.5 MHz, assignment aided by gHSQC, major rotamer) δ 12.5 (CH_3), 29.3 (C-13), 35.7 (C-5), 45.1 (C-1), 45.6 (C-3), 52.7 (OCH_3), 115.7 (CH), 118.6 (C-7), 119.3 (C), 120.2 (CH), 120.3 (CH), 124.5 (CH), 125.6 (CH), 126.2 (C), 126.3 (2CH), 129.1 (2CH), 133.3 (C), 133.6 (CH), 134.8 (C-6), 136.1 (C), 136.9 (C), 138.2 (C), 155.1 (CO); ESI-HRMS $[M+H]^+$ calcd for $C_{25}H_{25}N_2O_4S$ 449.1529, found 449.1523.

*4.5.2. 4-(Z)-Ethylidene-2-(methoxycarbonyl)-7-(phenylsulfonyl)-1,2,3,4,5,6-hexahydro-1,5-ethenoazocino[4,3-b]indole (**24**).* PPh_3 (13 mg, 0.05 mmol), Ag_2CO_3 (142 mg, 0.51 mmol), and $Pd(OAc)_2$ (4 mg, 0.017 mmol) were successively added to a solution of vinyl iodide **8** (98 mg, 0.17 mmol) in toluene (9 mL), and the resulting mixture was stirred at 80 °C for 1 h. The solvent was removed and the resulting residue was dissolved in CH_2Cl_2 (10 mL) and washed with H_2O (5 mL). The organic extracts were dried and concentrated and the resulting residue was chromatographed (from cyclohexane to 94:6 cyclohexane/CH_2Cl_2) to give **23** (14 mg, 19%) and the title compound **24** as a light brown oil: 33 mg (43%); ^{1}H NMR (400 MHz, assignment aided by gCOSY and gHSQC, 2:1 mixture of rotamers) δ 1.58 (major) and 1.65 (2d, J=6.4 Hz, 3H, CH_3), 3.27 (br s, 1H, 5-H), 3.30 (m, 2H, 6-H), 3.70 (major) and 3.76 (2s, 3H, OCH_3), 3.72 (m, 1H, 3-H), 4.43 and 4.67 (2d, J=15.2 Hz, 1H, 3-H), 5.39 (m, 1H, CH=ethylidene), 5.79 and 6.01 (major) (2d, J=7.6 or 8 Hz, 1H, 1-H), 6.16 (t, J=8.8 Hz, 1H, 13-H), 6.30 (m, 1H, 12-H), 7.26 (m, 2H), 7.40 (m, 2H), 7.53 (m, 1H), 7.70 (m, 3H), 8.20 (m, 1H); ^{13}C NMR (74.5 MHz, assignment aided by gHSQC, major rotamer) δ 13.2 (CH_3), 32.8 (C-6), 41.0 (C-3), 42.2 (C-5), 46.5 (C-1), 52.8 (OCH_3), 114.4 (CH), 117.0 (C), 118.7 (CH), 123.0 (CH ethylidene), 123.7 (CH), 124.5 (CH), 126.2 (2CH), 129.2 (2CH), 129.5 (C), 132.0 (C-12), 133.4 (C-13), 133.6 (CH), 134.9 (C), 135.9 (C), 138.4 (C), 139.1 (C), 156.1 (CO); ESI-HRMS $[M+H]^+$ calcd for $C_{25}H_{25}N_2O_4S$ 449.1529, found 449.1527.

*4.5.3. 4-(E)-Ethylidene-2-methyl-3-oxo-8-(phenylsulfonyl)-2,3,4,5-tetrahydro-1,5-methano-1H-azonino[4,3-b]indole (**25**).* PPh_3 (6 mg, 0.024 mmol), $Pd(OAc)_2$ (1 mg, 0.004 mmol), proton sponge (1.7 mg, 0.008 mmol), and K_2CO_3 (12 mg, 0.09 mmol) were successively added to a solution of vinyl bromide **13** (40 mg, 0.08 mmol) in toluene (5 mL), and the resulting mixture was heated at reflux for 20 h. The solvent was removed and the resulting residue was dissolved in CH_2Cl_2 (5 mL) and washed with H_2O (2×5 mL). The organic extracts were dried and concentrated and the resulting residue was chromatographed (95:5 hexanes/AcOEt) to give the title compound **25** as a light brown foam: 17 mg (50%); ^{1}H NMR (400 MHz, assignment aided by gHSQC) δ 1.90 (d, J=7.2 Hz, 3H), 2.11 (dd, J=13 and 2 Hz, 1H, 13-H), 2.60 (dm, J=13 Hz, 1H, 13-H), 2.82 (s, 3H, NCH_3), 3.95 (m, 1H, 5-H), 4.88 (d, J=6.5 Hz, 1H, 1-H), 5.95 (dd, J=12 and 6 Hz, 1H, 6-H), 6.90 (q, J=7.2 Hz, 1H), 7.30–7.40 (m, 4H), 7.55 (m, 3H), 7.65 (m, 2H), 8.25 (d, J=8 Hz, 1H); ^{13}C NMR (74.5 MHz, assignment aided by gHSQC) δ 13.9 (CH_3), 37.6 (C-13), 34.1 (NCH_3), 35.9 (C-5), 51.7 (C-1), 116.4 (CH), 117.0 (CH), 118.1 (C-7), 124.5 (C), 124.6 (CH), 125.6 (CH), 126.6 (2CH), 127.3 (C), 129.3 (2CH), 130.1 (C), 132.8 (CH), 134.0 (CH), 134.6 (C-6), 134.9 (C), 136.4 (C), 138.5 (C), 116.7 (CO); ESI-HRMS $[M+H]^+$ calcd for $C_{24}H_{23}N_2O_3S$ 419.1424, found 419.1412.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.04.022.

References and notes

1. Joule, J. A. In *Indoles, The Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; Wiley: New York, NY, 1983; Vol. 25, pp 232–239.
2. Andriantsiferana, M.; Besselièvre, R.; Riche, C.; Husson, H.-P. *Tetrahedron Lett.* **1977**, 2587–2590.
3. (a) Grierson, D. S.; Harris, M.; Husson, H.-P. *Tetrahedron* **1983**, *39*, 3683–3694; (b) Bosch, J.; Rubiralta, M.; Domingo, A.; Bolós, J.; Linares, A.; Minguillón, C.; Amat, M.; Bonjoch, J. *J. Org. Chem.* **1985**, *50*, 1516–1522; (c) Bosch, J.; Rubiralta, M.; Bolós, J. *Tetrahedron* **1987**, *43*, 391–396; (d) Salas, M.; Joule, J. A. *J. Chem. Res., Miniprint* **1990**, 664–673; (e) Rubiralta, M.; Marco, M.-P.; Bolós, J.; Trapé, J. *Tetrahedron* **1991**, *47*, 5585–5602.
4. For a more recent approach, see Amat, M.; Checa, B.; Llor, N.; Pérez, M.; Bosch, J. *Eur. J. Org. Chem.* **2011**, 898–907.
5. (a) Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Am. Chem. Soc.* **1993**, *115*, 5340–5341; (b) Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3597–3609; For the enantioselective version, see: (c) Bennasar, M.-L.; Zulaica, E.; Alonso, Y.; Bosch, J. *Tetrahedron: Asymmetry* **2003**, *14*, 469–479.
6. For general reviews, see: (a) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vol. 2; (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238.
7. For general reviews, see: (a) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-WCH: New York, NY, 2004; pp 217–316; (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644–4680.
8. For a preliminary communication of part of this work, see: Bennasar, M.-L.; Zulaica, E.; Solé, D.; Alonso, S. *Synlett* **2008**, 667–670.
9. For the construction of polycyclic systems by sequential RCM and aryl or heteroaryl halide Heck cyclizations, see: (a) Grigg, R.; Sridharan, V.; York, M. *Tetrahedron Lett.* **1998**, *39*, 4139–4142; (b) Grigg, R.; York, M. *Tetrahedron Lett.* **2000**, *41*, 7255–7278; (c) Lautens, M.; Zunic, V. *Can. J. Chem.* **2004**, *82*, 399–407; (d) Enders, D.; Lenzen, A.; Backes, M.; Janeck, C.; Catlin, K.; Lannou, M.-I.; Runsink, J.; Raabe, G. *J. Org. Chem.* **2005**, *70*, 10538–10551; (e) Sunderhaus, J. D.; Dockendorff, C.; Martin, S. F. *Org. Lett.* **2007**, *9*, 4223–4226; (f) Ribelin, T. P.; Judd, A. S.; Akritopoulou-Zanze, I.; Henry, R. F.; Cross, J. L.; Whittern, D. N.; Djuric, S. W. *Org. Lett.* **2007**, *9*, 5119–5122.
10. (a) Rawal, V. H.; Michoud, C. *Tetrahedron Lett.* **1991**, *32*, 1695–1698; (b) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc.* **1993**, *115*, 3030–3031; (c) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685–2686; (d) Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidró, E.; Bosch, J. *Chem.—Eur. J.* **2000**, *6*, 655–665; (e) Eichberg, M. J.; Dorta, R. L.; Grotjahn, D. B.; Lamottke, K.; Schmidt, M.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **2001**, *123*, 9324–9337; (f) Mori, M.; Nakanishi, M.; Kahishima, D.; Sato, Y. *J. Am. Chem. Soc.* **2003**, *125*, 9801–9807; (g) Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2008**, *130*, 5368–5377; (h) Martin, D. B. C.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 3472–3473.
11. Birman, V. B.; Rawal, V. H. *J. Org. Chem.* **1998**, *63*, 9146–9147.
12. (a) Bennasar, M.-L.; Zulaica, E.; Solé, D.; Alonso, S. *Chem. Commun.* **2009**, 3372–3374; (b) Bennasar, M.-L.; Zulaica, E.; Solé, D.; Roca, T.; García-Díaz, D.; Alonso, S. *J. Org. Chem.* **2009**, *74*, 8359–8368.
13. Bennasar, M.-L.; Solé, D.; Zulaica, E.; Alonso, S. *Org. Lett.* **2011**, *13*, 2042–2045.
14. For instance, see: (a) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T.; Takeda, E. *Tetrahedron* **1983**, *39*, 3657–3668; (b) Gràcia, J.; Casamitjana, N.; Bonjoch, J.; Bosch, J. *J. Org. Chem.* **1994**, *59*, 3939–3951; (c) Saito, M.; Kawamura, M.; Hiroya, K.; Ogasawara, K. J. *Chem. Commun.* **1997**, 765–766.
15. Bennasar, M.-L.; Zulaica, E.; Solé, D.; Alonso, S. *Tetrahedron* **2007**, *63*, 861–866.
16. Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1987**, *52*, 104–109.
17. Hagiwara, H.; Choshi, T.; Nobuhiro, J.; Fujimoto, H.; Hibino, S. *Chem. Pharm. Bull.* **2001**, *49*, 881–886.
18. (a) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667–2670; (b) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113–10130.

19. Rutherford, J. L.; Rainka, M. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 15618–15619.
20. See also: (a) Solé, D.; Urbaneja, X.; Bonjoch, J. *Tetrahedron Lett.* **2004**, *45*, 3131–3135; (b) Solé, D.; Urbaneja, X.; Bonjoch, J. *Adv. Synth. Catal.* **2004**, *346*, 1646–1650.
21. The configuration of the ethylidene substituent was established by NOESY experiments.
22. (a) Rawal, V. H.; Michoud, C. *J. Org. Chem.* **1993**, *58*, 5583–5584; (b) Feutren, S.; McAlonan, H.; Montgomery, D.; Stevenson, P. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1129–1137.
23. Owczarczyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E. *J. Am. Chem. Soc.* **1992**, *114*, 10091–10092.
24. A seven-membered palladacycle formed by coordination of a sulfonyl oxygen atom has been proposed as a potential transition state in some Suzuki reactions: Broutin, P.-E.; Colobert, F. *Org. Lett.* **2005**, *7*, 3737–3740.
25. Miyaura, N.; Ishikawa, M.; Suzuki, A. *Tetrahedron Lett.* **1992**, *33*, 2571–2574.
26. Solé, D.; Urbaneja, X.; Cordero-Vargas, A.; Bonjoch, J. *Tetrahedron* **2007**, *63*, 10177–10184.
27. Bachman, G. B. *J. Am. Chem. Soc.* **1933**, *55*, 4279–4284.