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Synthesis of cleavamine-type indole alkaloids and their 5-nor derivatives by a ring-closing metathesis–vinyl halide Heck cyclization strategy

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ABSTRACT

An indole-templated RCM has been used to assemble the central medium-sized rings of the indole *upper-half* of vinorelbine and the cleavamine-type alkaloids. From these key intermediates, the bridged tetracyclic framework of the alkaloids is completed with the insertion of a 2-ethylpropeno unit, by N-alkylation followed by a challenging *endocyclic* vinyl halide Heck cyclization. The usefulness of the approach is illustrated with the synthesis of (±)-cleavamine and (±)-dihydrocleavamine.

1. Introduction

The remarkable structural diversity of indole alkaloids as well as their significant biological activities have long caught the attention of synthetic organic chemists, providing inspiration for the development of novel synthetic strategies. Our longstanding interest in this area led us to envisage a combination of two well-established C–C bond-forming reactions, a ring-closing metathesis (RCM),[1] and a Heck cyclization,[2] for the rapid assembly of the bridged tetracyclic topography of some indole alkaloids. Based on this strategy, we have recently developed a unique approach to the alkaloids ervitsine[3] and apparicine.[4] In particular, we have shown that after an indole-templated RCM to build the central medium-sized ring of these alkaloids, a vinyl halide Heck coupling accomplishes the closure of the piperidine ring with the concomitant placement of the exocyclic 20*E*-ethylidene substituent (Fig. 1). Other authors have also made use of similar *exocyclic* vinyl halide Heck couplings for the assembly of the bridged core of indole alkaloids including pentacyclic *Strychnos* alkaloids,[5] strychnine,[6] and minfiensine.[7]

As an extension of our earlier work, we considered applying the RCM–Heck double annulation strategy for the construction of other bridged indolic structures, such as those included in cleavamines and their 5-nor derivatives (Fig. 2). The cleavamine-type alkaloids

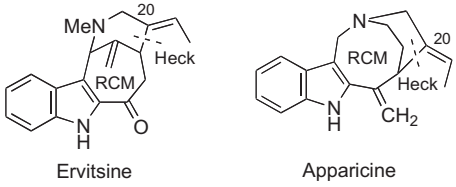

Fig. 1. Previous applications of the RCM–Heck cyclization strategy.

(cleavamine, velbanamine, or (+)-20*R*-dihydrocleavamine) are a small subgroup of tetracyclic natural bases belonging to the *Iboga* family[8] that are structurally characterized by a central nine-membered ring and a bridged 3-substituted piperidine moiety, featuring a 1-azabicyclo[6.3.1]dodecane framework. The same tetracyclic skeleton is also found in the *Aspidosperma* alkaloid quebrachamine. Cleavamines are of particular interest not only because they have provided key synthetic intermediates for pentacyclic *Iboga* derivatives[9] but also because they constitute the indole *upper-half* of the well known antimitotic bisindole *Catharanthus* alkaloids vinblastine and vincristine.[10] On the other hand, the 5-nor tetracyclic architecture, featuring a 1-azabicyclo[5.3.1]undecane bridged system, constitutes the indole *upper-half* of the semisynthetic derivative vinorelbine (5′-noranhydrovinblastine), also used in cancer chemotherapy.[10,11]

As depicted in Scheme 1, our synthetic plan for the assembly of the bridged arrangements of the above alkaloids (**I**) commenced

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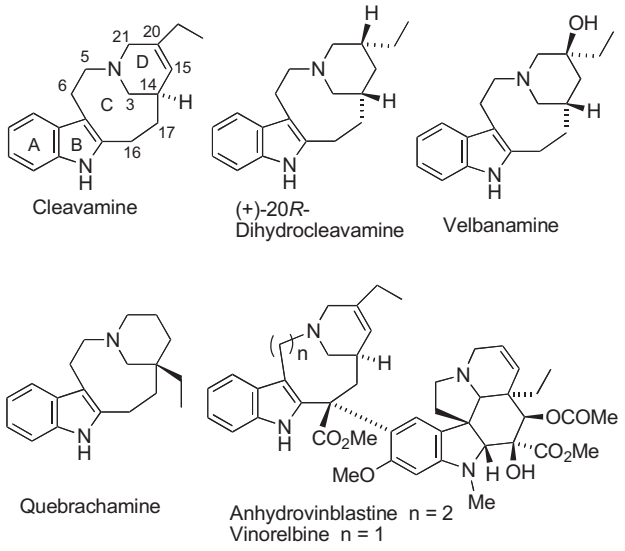
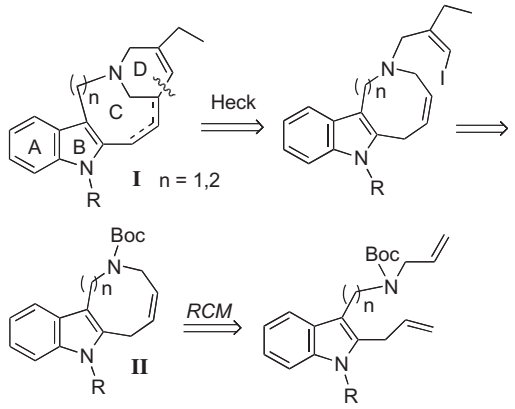


Fig. 2. Cleavamine, *Catharanthus*, and related alkaloids.



Scheme 1. Synthetic strategy.

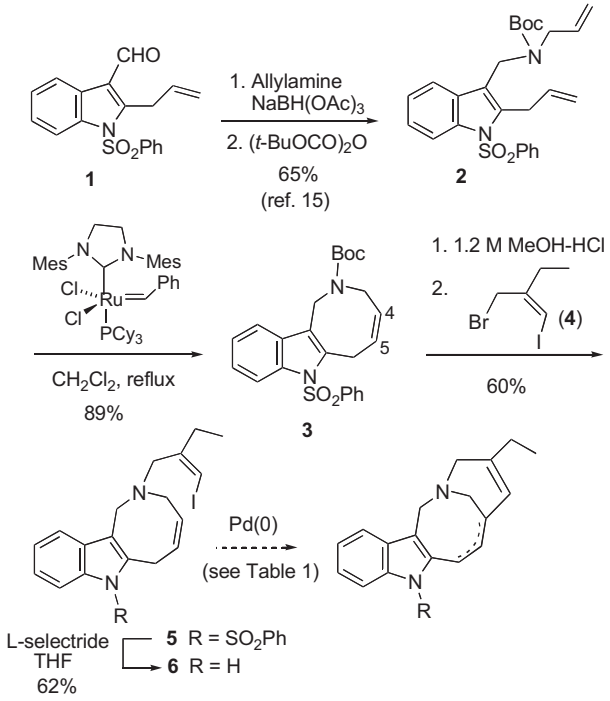
with the metathetic closure of appropriate 2,3-dialkenyl indoles to provide the tricyclic ABC substructures **II**, containing a central eight- or nine-membered ring.[12] From these pivotal intermediates, the carbon skeleton would be completed with the insertion of a 2-ethylpropeno unit by N-alkylation followed by a challenging *endocyclic* vinyl halide Heck cyclization upon the double bond left by the RCM step. It should be noted that, apart from our own work on the synthesis of apparicine,[4] Heck cyclizations upon cyclooctenes or cyclononenes to produce strained bridged systems are rare, most reported examples dealing with cyclizations from more robust aryl halides.[13]

This article describes the development of the above annulation chemistry for the assembly of the 5-nor cleavamine skeleton and the formulation of a novel synthetic approach to the alkaloids cleavamine and dihydrocleavamine.[14]

2. Results and discussion

2.1. Heck cyclization upon azocino[4,3-*b*]indoles: access to 5-nor cleavamines

We set out to study the construction of the 1-azabicyclo[5.3.1]undecane bridged system (**I**, n=1, Scheme 1), which defines the indole *upper-half* of vinorelbine, targeting azocino[4,3-*b*]indole **3** (Scheme 2), with the 4,5-double bond functionality required for the subsequent Heck coupling. This compound was easily prepared applying a slight modification of our previously reported procedure.[15] Thus, reductive amination of aldehyde **1** with allylamine followed by protection of the resulting secondary amine with a Boc group gave carbamate **2**, which smoothly underwent RCM in the presence of the second-generation Grubbs catalysts to give **3** in 58% overall yield. At this point, access to the more advanced synthetic intermediate **5** required the manipulation of the aliphatic nitrogen to install the haloalkenyl chain. The *N*-Boc group was successfully removed using a mild acid protocol (1.2 M HCl in MeOH at rt) and the resulting secondary amine was directly alkylated with allylic bromide **4**[16] to give **5** in 60% overall yield. We also considered of interest to prepare the respective indole-deprotected substrate **6**, which was accomplished by treatment of **5** with L-Selectride in refluxing THF (62% yield). This reductive protocol was chosen to minimize both the previsible isomerization of the double bond to its indole-conjugated counterpart[4] and the previsible elimination of the haloalkenyl chain under the standard basic conditions.

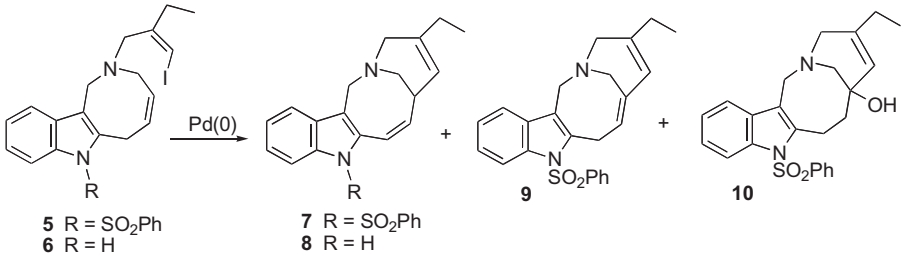


Scheme 2. Access to the 1-azabicyclo[5.3.1]undecane bridged system.

A detailed investigation into the Heck reaction was then undertaken using vinyl iodide **5** as the main substrate (Table 1). We first examined the reaction under a cationic protocol ($Pd(OAc)_2$, PPh_3, Ag_2CO_3, entry 1) similar to that successfully applied in our synthesis of apparicine,[4] but only the unchanged material was recovered using either refluxing toluene or acetonitrile as solvent. Without the additive Ag_2CO_3, the inclusion of proton-sponge® as base led to minor amounts of tetracycle **7**, coming from the expected *exo* cyclization with the generation of a disubstituted indole-conjugated double bond (entry 2). More satisfactorily, the yield of **7** increased to 40% using $Pd(PPh_3)_4$ as the palladium catalyst (entry 3). In both cases, minor amounts of another cyclized product, not stable enough to be characterized, were detected in the reaction mixtures.

The application of the latter conditions to the *N*-unsubstituted indolic substrate **6** resulted in a cleaner cyclization, producing tetracycle **8** as the only product in 45% yield (entry 4). This compound could be alternatively obtained by removal of the *N*-phenylsulfonyl group of tetracycle **7** under standard basic conditions (67%,

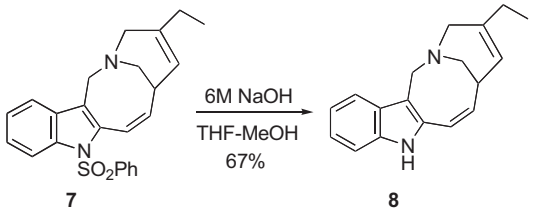
Table 1
Heck cyclization of vinyl iodides **5** and **6**



Entry	Substrate	Conditions	Products[a] (yield %)
1	**5**	$Pd(OAc)_2$ (10%), PPh_3 (30%), Ag_2CO_3 (2 equiv), toluene, or CH_3CN, reflux, 24 h	**5** (60)
2	**5**	$Pd(OAc)_2$ (10%), PPh_3 (40%), proton-sponge®[b] (0.3 equiv), K_2CO_3 (1.5 equiv), toluene, reflux, 24 h	**5** (45), **7** (15)[c]
3	**5**	$Pd(PPh_3)_4$ (15%), proton-sponge® (0.1 equiv), K_2CO_3 (1.5 equiv), toluene, reflux 24 h	**7** (40)[b]
4	**6**	$Pd(PPh_3)_4$ (15%), proton-sponge® (0.1 equiv), K_2CO_3 (1.5 equiv), toluene, reflux 24 h	**8** (45)
5	**5**	$Pd_2(dba)_3$ (7.5%), xantphos (15%), proton-sponge® (0.3 equiv), K_2CO_3 (1.5 equiv), toluene, reflux, 24 h	**7** (25), **9** (24), **10** (20)

[a] Isolated yields after column chromatography.
[b] *N*,*N*,*N*′,*N*′-Tetramethyl-1,8-naphthalenediamine.
[c] Minor amounts (10–15%) of an unidentified cyclization product were also formed.

Scheme 3). All attempts to selectively remove the disubstituted double bond of **8** by catalytic hydrogenation met with failure.



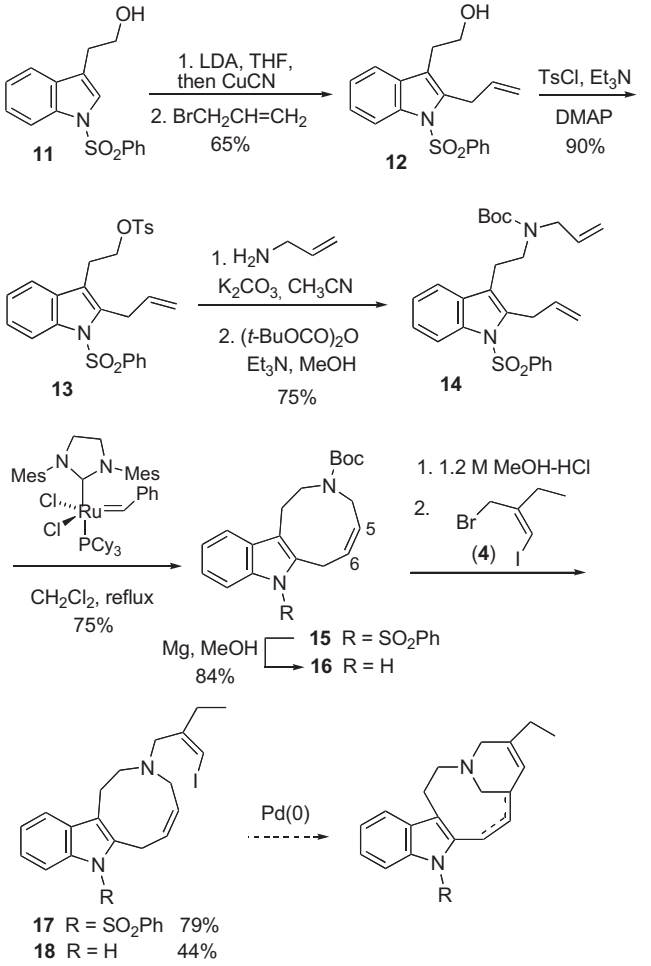
Scheme 3. Indole deprotection of tetracycle **7**.

On the other hand, the cyclization followed a different course in the presence of $Pd_2(dba)_3$ and the bidentate ligand xantphos, in which case vinyl iodide **5** led to a nearly equimolecular mixture of **7**, its double bond isomer **9**, and carbinol **10** in a higher cyclization yield (70%, entry 5). Carbinol **10** comes from the hydration of the strained bridgehead double bond of **9**, which is probably the result of a direct β-hydride elimination from the initially formed σ-alkyl palladium intermediate rather than an isomerization process from **7**. The different regioselectivity in the β-elimination step in the presence of xantphos proved to be crucial for our successful Heck cyclization in the higher homologous series (see below).

While the ^1H NMR spectra of tetracycles **8**, **9**, and **10** exhibited clear resonances at room temperature, which allowed their uneventful structural determination, tetracycle **7** showed broad signals, implying the existence of two conformational states in solution with a high barrier to interconversion. Upon inspection of the ^1H NMR at a lower temperature (−30 °C) two sets of clear signals in a 2:1 ratio were observed. The assignment was completed by analysis of ^{13}C NMR data (−10 °C) with the aid of bidimensional techniques (HSQC).

2.2. Synthesis of cleavamines

Attention was then focused on the application of the RCM–Heck cyclization strategy to assemble the 1-azabicyclo[6.3.1]dodecane bridged framework (**I**, *n*=2, Scheme 1), which defines the tetracyclic architecture of the cleavamine alkaloids.[14] As stated before, the sequential ring formation would start with the construction of a suitable azonino[5,4-*b*]indole incorporating a double bond at the 5,6-position (e.g., **15** or **16**, Scheme 4) and conclude with the formation of the 3-ethylpiperidine ring.



Scheme 4. Access to the 1-azabicyclo[6.3.1]dodecane bridged system.

The synthetic route to the key intermediate **15** began with the preparation of the diene precursor **14** by successive introduction of the required alkenyl appendages from the known tryptophol **11**,[17] which was equipped with a robust phenylsulfonyl at the indole

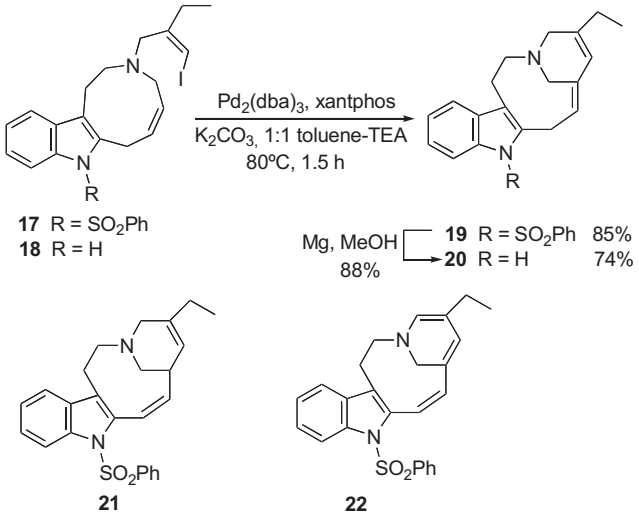
nitrogen as in the above series. Exposure of **11** to excess LDA and CuCN followed by reaction of the intermediate organocopper with allyl bromide led to 2-allylindole **12** (65%). This was uneventfully converted into diene **14** by treatment of the corresponding tosylate **13** with allylamine and subsequent protection of the resulting secondary amine (75% for the two steps).

The next issue to be tackled was the closure of the nine-membered by RCM.[13b,18] We expected that, as in our previous synthesis of azocinoindoles,[4,15] both the fused indole ring and the nitrogen carbamate would operate synergistically, thus favoring the desired cyclization. Satisfactorily, RCM of diene **14** proceeded smoothly in the presence of the second-generation Grubbs catalyst in refluxing CH_2Cl_2. The reaction was completed in a short reaction time (2 h 30 min) and azoninoindole **15**, with the *Z* configuration of the double bond, was isolated in 75% yield.

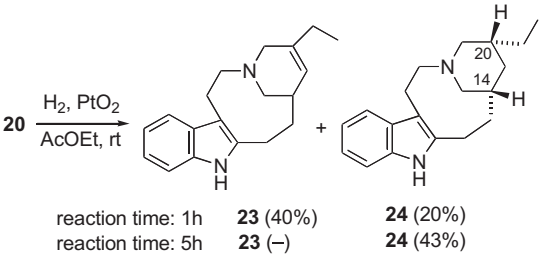
Our following task was to install the haloalkenyl chain required for the subsequent Heck reaction. Thus, removal of the Boc group of **15** in mild acid conditions and direct alkylation of the resulting secondary amine with bromide **4** as in the above series led to vinyl iodide **17** in 79% overall yield. In turn, the respective indole-deprotected substrate **18** was prepared from **15** by reductive removal of the phenylsulphonyl group using Mg in MeOH (84%), followed by derivatization of the aliphatic nitrogen of the resulting compound **16** according to the usual protocol (44%).

The availability of substrate **17** allowed us to examine the intramolecular coupling of the vinyl iodide and the disubstituted double bond included in the azonine ring to complete the bridged tetracyclic framework of cleavamines. We expected tetracycle **21** to be preferentially formed as a result of an *exo* cyclization with generation of an indole-conjugated double bond. However, under a variety of conditions, including palladium precatalysts [$Pd(PPh_3)_4$, Pd_2dba_3], ligands (BINAP, dppe), and additives (proton-sponge, Et_3N, diisopropylethylamine) in refluxing toluene, we only obtained mixtures of the starting material and variable amounts of tetracycle **22**, which presumably arose from **21** by oxidation. Although we were able to isolate **21** using shorter reaction times or lower temperatures, it proved to be highly unstable, slowly being converted into **22** under the extractive workup or column chromatography.[19] We then examined the Heck cyclization in the presence of the phosphine xantphos, expecting a different regioselectivity in the elimination step as in our previous synthesis of 5-nor cleavamines, which would avoid the undesirable formation of **22**. To our delight, the outcome of the cyclization changed completely on exposure of **17** to Pd_2dba_3/xantphos and K_2CO_3 in toluene–Et_3N at 80 °C for a short reaction time (1.5 h). Tetracycle **19**, embodying a trisubstituted bridgehead double bond, was isolated in a yield as high as 85%. In contrast to its regioisomer **21**, tetracycle **19** showed no tendency to undergo oxidation. The application of this protocol to the indole-deprotected substrate **18** similarly led to tetracycle **20** (74%), which was alternatively obtained by deprotection of **19** (88%) under reductive conditions (Scheme 5).

With the 1-azabicyclo[6.3.1]dodecane framework in hand, the synthesis of (±)-cleavamine only required the selective reduction of the bridgehead double bond. When tetracycle **20** was subjected to catalytic hydrogenation in AcOEt, (±)-cleavamine (**23**) was isolated as the major product (40% yield) after a short reaction time (1 h), although minor amounts of 14,20-*cis*-dihydrocleavamine (**24**) were also formed (Scheme 6). As expected, longer reaction times (5 h) gave **24** as the only product (43%). Synthetic cleavamines displayed ^1H and ^{13}C NMR spectral data identical to that reported for the natural products.[20,21]



Scheme 5. Heck cyclization of vinyl halides **17** and **18**.



Scheme 6. Completion of the synthesis of cleavamines.

3. Conclusions

We have developed a concise entry to the strained tetracyclic arrangement of the cleavamine alkaloids and their 5-nor derivatives combining an RCM with an *endocyclic* vinyl halide Heck cyclization. The synthesis of (±)-cleavamine and (±)-dihydrocleavamine significantly expands the scope and potential of this double annulation strategy for the synthesis of bridged 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. Unless otherwise indicated, 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 5-nor cleavamines

*4.2.1. 2-(tert-Butoxycarbonyl)-7-(phenylsulfonyl)-1,2,3,6-tetrahydroazocino[4,3-b]indole (**3**).*[15] The second-generation Grubbs catalyst (23 mg, 0.026 mmol) was added under Ar to a solution of diene **2**[15] (180 mg, 0.38 mmol) in CH_2Cl_2 (10 mL) and the resulting mixture was heated at reflux for 2 h. The reaction mixture was concentrated

and the residue was chromatographed (1:1 hexanes/AcOEt) to give the title compound **3** as a white foam: 0.34 g (89%).

*4.2.2. 2-(2-Ethyl-3-iodo-2-propenyl)-7-(phenylsulfonyl)-1,2,3,6-tetrahydroazocino[4,3-b]indole (**5**).* A solution of carbamate **3** (450 mg, 1.03 mmol) in 1.2 M HCl in MeOH (4.2 mL) was stirred at rt for 18 h. The reaction mixture was basified with 20% NH_4OH and concentrated. The residue was partitioned between CH_2Cl_2 and H_2O and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give the crude secondary amine (278 mg). Diisopropylethylamine (0.2 mL, 1.16 mmol) and (*Z*)-2-(bromomethyl)-1-iodo-1-butene[16] (**4**, 235 mg, 0.82 mmol) were added to a solution of the above amine in 1:1 CH_2Cl_2/acetonitrile (16 mL) and the resulting mixture was stirred at rt overnight. The solvent was removed and the residue was dissolved in CH_2Cl_2 and washed with 10% aqueous $NaHCO_3$. The organic solution was dried and concentrated to give the crude product. After column chromatography (8:2 hexanes/AcOEt), the title compound **5** was obtained as an oil: 327 mg (60%); ^{1}H NMR (400 MHz) δ 1.06 (t, *J*=7.6 Hz, 3H), 2.29 (q, *J*=7.6 Hz, 2H), 3.07 (d, *J*=6.8 Hz, 2H); 3.26 (s, 2H), 3.90 (s, 2H), 4.05 (d, *J*=6 Hz, 2H), 5.60 (m, 1H), 5.99 (m, 1H), 6.04 (br s, 1H), 7.28 (m, 2H), 7.40 (m, 3H), 7.54 (dd, *J*=7.6 and 7.2 Hz, 1H), 7.76 (dd, *J*=8.8 and 1.2 Hz, 2H), 8.23 (dd, *J*=8.4 and 0.8 Hz, 1H); ^{13}C NMR (74.5 MHz) δ 12.6 (CH_3), 26.6 (CH_2), 29.5 (CH_2), 47.0 (CH_2), 49.1 (CH_2), 60.6 (CH_2), 76.7 (CH), 115.0 (CH), 117.0 (C), 118.0 (CH), 123.7 (CH), 124.3 (CH), 126.2 (2 CH), 126.6 (CH), 129.0 (C), 129.2 (2 CH), 129.5 (CH), 133.6 (CH), 136.4 (C), 137.1 (C), 139.0 (C), 150.6 (C); ESI-HRMS $[M+H]^+$ calcd for $C_{24}H_{26}IN_2O_2S$ 533.0754, found 533.0757.

*4.2.3. 5-(2-Ethyl-3-iodo-2-propenyl)-1,2,3,6-tetrahydroazocino[4,3-b]indole (**6**).* L-Selectride (0.66 mL of 1 M solution in THF, 0.66 mmol) was added under Ar to a solution of azocinoindole **5** (35 mg, 0.066 mmol) in THF (5 mL). After being heated at reflux for 1 h, the reaction mixture was quenched with MeOH, diluted with H_2O, and extracted with AcOEt. The organic extracts were washed with brine, dried, and concentrated and the resulting residue was purified by column chromatography (from CH_2Cl_2 to 97:3 CH_2Cl_2/MeOH) to give **6** as an oil: 16 mg (62%); ^{1}H NMR (400 MHz) δ 1.10 (t, *J*=7.6 Hz, 3H), 2.41 (qd, *J*=7.6 and 1.2 Hz, 2H), 3.14 (d, *J*=7.6 Hz, 2H), 3.35 (s, 2H), 3.70 (d, *J*=4.8 Hz, 2H), 3.97 (s, 2H), 5.79 (q, *J*=7.6 Hz, 1H), 6.00–6.12 (m, 2H), 7.07–7.15 (m, 2H), 7.27 (dd, *J*=6 and 1.6 Hz, 1H), 7.50 (dd, *J*=6.8 and 1.6 Hz, 1H), 7.87 (br, 1H); ^{13}C NMR (100.5 MHz) δ 12.6 (CH_3), 27.7 (CH_2), 29.5 (CH_2), 45.9 (CH_2), 48.0 (CH_2), 60.7 (CH_2), 77.2 (CH), 110.0 (CH), 117.7 (CH), 119.6 (CH), 121.3 (CH), 126.9 (br CH), 128.8 (br CH), 129.5 (C), 134.8 (C), 135.3 (C), 150.5 (C), one quaternary C was not observed; ESI-HRMS $[M+H]^+$ calcd for $C_{18}H_{22}IN_2$ 393.0822, found 393.0823.

*4.2.4. Heck cyclization of vinyl iodide **5**. Table 1, entry 3.* $Pd(PPh_3)_4$ (15 mg, 0.013 mmol), proton-sponge® (5.5 mg, 0.025 mmol), and K_2CO_3 (18 mg, 0.13 mmol) were added under Ar to a solution of vinyl iodide **5** (45 mg, 0.085 mmol) in toluene (8.5 mL), and the resulting solution was heated at reflux for 24 h. The solvent was removed and the residue was partitioned between CH_2Cl_2 and a saturated aqueous $NaHCO_3$ solution. The organic layer was dried and concentrated and the resulting residue was purified by column chromatography (from CH_2Cl_2 to 98:2 CH_2Cl_2/MeOH). A second column chromatography (from Et_2O to 99:1 Et_2O/diethylamine) led to *4-ethyl-9-(phenylsulfonyl)-1,2,3,6-tetrahydro-2,6-methanoazecino[4,3-b]indole* (**7**) as an oil: 14 mg (40%); ^{1}H NMR (500 MHz, −30 °C, *major conformer*) δ 0.99 (t, *J*=7.5 Hz, 3H), 1.93 (m, 2H), 2.40 (dd, *J*=14 and 4.5 Hz, 1H), 2.59 (d, *J*=14 Hz, 1H), 2.70 (br s, 1H), 3.05 (d, *J*=17.5 Hz, 1H), 3.66 (d, *J*=17.5 Hz, 1H), 3.72 (d, *J*=11 Hz, 1H), 3.77 (d, *J*=11 Hz, 1H), 5.60 (s, 1H), 5.90 (dd, *J*=12.5 and 4.5 Hz, 1H), 6.70 (d, *J*=12.5 Hz, 1H), 7.20–7.75 (m, 8H), 8.19 (d, *J*=8.5 Hz, 1H); *minor conformer*: −0.55 (t, *J*=7.5 Hz, 3H), 0.62 (m, 1H), 0.79 (m, 1H), 2.59 (masked, 1H), 2.78 (d, *J*=18 Hz, 1H), 3.00–3.10 (m, 3H), 3.20 (d, *J*=15 Hz, 1H), 3.91 (s, 1H), 4.61 (d, *J*=15 Hz, 1H), 6.30 (dd, *J*=12 and 9 Hz, 1H), 7.02 (d, *J*=12 Hz, 1H), 7.20–7.75 (m, 7H), 7.85 (d, *J*=8 Hz, 1H), 8.21 (d, *J*=10 Hz, 1H); ^{13}C NMR (100.6 MHz, −10 °C, *major conformer*) δ 11.8 (CH_3), 27.9 (CH_2), 34.3 (CH), 43.8 (CH_2), 44.9 (CH_2), 55.5 (CH_2), 115.2 (CH), 115.8 (CH), 116.9 (C), 118.6 (C), 118.8 (CH), 120.9 (CH), 124.3 (CH), 125.2 (CH), 126.3 (2 CH), 128.8 (2 CH), 130.0 (C), 133.8 (CH), 135.3 (C), 135.8 (CH), 136.5 (C), 136.9 (C); *minor conformer*: 11.0 (CH_3), 27.4 (CH_2), 32.9 (CH), 48.9 (CH_2), 49.1 (CH_2), 53.5 (CH_2), 114.1 (CH), 117.4 (CH), 119.9 (CH), 123.4 (CH), 124.5 (CH), 126.0 (CH), 127.1 (2 CH), 129.2 (2 CH), 130.7 (C), 131.9 (CH), 134.0 (C), 137.4 (CH), 138.6 (C), three quaternary C were not observed; ESI-HRMS $[M+H]^+$ calcd for $C_{24}H_{25}N_2O_2S$ 405.1631, found 405.1628.

Table 1, entry 5. $Pd_2(dba)_3$ (5.5 mg, 0.006 mmol), xantphos (7 mg, 0.012 mmol), proton-sponge® (5 mg, 0.023 mmol), and K_2CO_3 (16.5 mg, 0.12 mmol) were added under Ar to a solution of vinyl iodide **5** (42 mg, 0.079 mmol) in toluene (8 mL), and the resulting solution was heated at reflux for 24 h. Workup as above and column chromatography (from CH_2Cl_2 to 94:6 CH_2Cl_2/MeOH) gave **7** (8 mg, 25%), **9** (7.7 mg, 24%), and **10** (6.7 mg, 20%). *4-Ethyl-9-(phenylsulfonyl)-1,2,3,8-tetrahydro-2,6-methanoazecino[4,3-b]indole* (**9**): oil; ^{1}H NMR (500 MHz) δ 0.99 (t, *J*=7.5 Hz, 3H), 1.91 (q, *J*=7.5 Hz, 2H), 2.90 (d, *J*=18 Hz, 1H), 3.03 (d, *J*=12.5 Hz, 1H), 3.32 (d, *J*=12.5 Hz, 1H), 3.49 (d, *J*=12 Hz, 1H), 3.70 (dd, *J*=19 and 5.5 Hz, 1H), 3.70 (m, 2H), 3.83 (dd, *J*=19 and 8 Hz, 1H), 5.73 (dd, *J*=8 and 5 Hz, 1H), 6.05 (s, 1H), 7.19–7.24 (m, 2H), 7.33 (t, *J*=7.5 Hz, 2H), 7.45 (tt, *J*=7.5 and 1.5 Hz, 1H), 7.50 (dd, *J*=7.5 and 1.5 Hz, 1H), 7.61 (m, 2H), 8.16 (d, *J*=7.5 Hz, 1H); ^{13}C NMR (125.7 MHz, HSQC) δ 12.1 (CH_3), 26.7 (CH_2), 27.6 (CH_2), 44.1 (CH_2), 49.2 (CH_2), 56.8 (CH_2), 114.7 (CH), 117.5 (CH), 118.0 (CH), 122.3 (CH), 123.6 (CH), 124.6 (CH), 126.1 (2 CH), 128.9 (C), 129.3 (2 CH), 131.0 (C), 133.5 (C), 133.7 (CH), 136.4 (C), 137.6 (C), 139.2 (C), one quaternary C was not observed; ESI-HRMS $[M+H]^+$ calcd for $C_{24}H_{25}N_2O_2S$ 405.1631, found 405.1630. *4-Ethyl-6-hydroxy-9-(phenylsulfonyl)-1,2,3,6,7,8-hexahydro-2,6-methanoazecino[4,3-b]indole* (**10**): oil; ^{1}H NMR (300 MHz) δ 0.80 (t, *J*=7.5 Hz, 3H), 1.56 (dq, *J*=8.4 and 7.5 Hz, 1H), 1.71 (dq, *J*=8.4 and 7.5 Hz, 1H), 1.89 (ddd, *J*=13.8, 8.1, and 3 Hz, 1H), 2.08 (ddd, *J*=13.8, 9.9, and 3 Hz, 1H), 2.89 (d, *J*=14.7 Hz, 1H), 2.98 (d, *J*=17.4 Hz, 1H), 3.10 (ddd, *J*=12, 8.1, and 3 Hz, 1H), 3.15 (d, *J*=14.7 Hz, 1H), 3.38 (ddd, *J*=12, 9.9, and 3 Hz, 1H), 3.52 (d, *J*=17.4 Hz, 1H), 3.91 (d, *J*=13.5 Hz, 1H), 4.00 (d, *J*=13.5 Hz, 1H), 5.18 (s, 1H), 7.24–7.33 (m, 2H), 7.42 (dd, *J*=7.6 and 1.2 Hz, 2H), 7.53 (tt, *J*=7.6 and 1.2 Hz, 1H), 7.57 (d, *J*=8 Hz, 1H), 7.76 (m, 2H), 8.21 (dd, *J*=7.2 and 1.2 Hz, 1H); ^{13}C NMR (125.7 MHz, HSQC) δ 11.2 (CH_3), 21.8 (CH_2), 27.6 (CH_2), 39.4 (CH_2), 46.5 (CH_2), 52.4 (br CH_2), 56.3 (CH_2), 67.7 (C), 114.7 (CH), 118.6 (CH), 123.9 (CH), 124.8 (CH), 125.2 (CH), 126.2 (2 CH), 128.8 (C), 129.4 (2 CH), 133.9 (CH), 136.3 (C), 139.1 (C), three quaternary C were not observed; ESI-HRMS $[M+H]^+$ calcd for $C_{24}H_{27}N_2O_3S$ 423.1737, found 423.1735.

*4.2.5. 4-Ethyl-1,2,3,6-tetrahydro-2,6-methanoazecino[4,3-b]indole (**8**). From vinyl iodide* **6**. Vinyl iodide **6** (20 mg, 0.05 mmol) in toluene (4.5 mL) was allowed to react with $Pd(PPh_3)_4$ (11.5 mg, 0.01 mmol), proton-sponge® (2.1 mg, 0.01 mmol), and K_2CO_3 (10 mg, 0.075 mmol) as described in Table 1, entry 3. After being heated at reflux for 16 h, the usual workup and column chromatography (from Et_2O to 98:2 Et_2O/diethylamine) gave tetracycle **8** as an oil: 6 mg (45%); ^{1}H NMR (400 MHz) δ 0.89 (t, *J*=7.6 Hz, 3H), 1.87 (m, 2H), 2.85 (dd, *J*=12.4 and 5.6 Hz, 1H), 2.87 (br s, 1H), 3.15 (d, *J*=17.2 Hz, 1H), 3.35 (d, *J*=12.4 Hz, 1H), 3.69 (d, *J*=17.2 Hz, 1H), 3.90 (d, *J*=12.8 Hz, 1H), 4.11 (d, *J*=12.8 Hz, 1H), 5.51 (s, 1H), 5.95 (dd, *J*=12 and 5.6 Hz, 1H), 6.33 (d, *J*=12 Hz, 1H), 7.09–7.17 (m, 2H), 7.30 (d, *J*=7.6 Hz, 1H), 7.67 (d, *J*=8.4 Hz, 1H), 8.07 (br, 1H); ^{13}C NMR (100.5 MHz) δ 11.8 (CH_3), 28.1 (CH_2), 34.6 (CH), 43.3 (CH_2), 46.2 (CH_2), 54.0 (CH_2), 110.6 (CH), 116.7 (CH), 117.7 (C), 118.6 (CH), 120.0

(CH), 120.7 (CH), 122.2 (CH), 128.2 (C), 135.3 (C), 135.8 (CH), 135.9 (C), 136.5 (C); ESI-HRMS $[M+H]^+$ calcd for $C_{18}H_{21}N_2$ 265.1699, found 265.1698.

From tetracycle **7**. 6 M aqueous NaOH solution (2 mL) was added to a solution of tetracycle **7** (18 mg, 0.044 mmol) in a 1:3 mixture of THF/MeOH (6 mL). After being heated at 85 °C for 3 h, the reaction mixture was poured into a saturated aqueous NH_4Cl solution. The organic solvent was removed and the resulting residue was partitioned between CH_2Cl_2 and brine. The organic layer was dried and concentrated and the residue was purified by column chromatography (from Et_2O to 98:2 Et_2O/diethylamine) to give **8**: 8 mg (67%).

4.3. Synthesis of cleavamines

*4.3.1. 2-Allyl-3-(2-hydroxyethyl)-1-(phenylsulfonyl)indole (**12**).* A solution of diisopropylamine (0.7 mL, 4.99 mmol) in THF (21 mL) was cooled to −78 °C and *n*-BuLi (2.5 M in hexanes, 1.8 mL, 4.5 mmol) was slowly added. The resulting solution was stirred at −78 °C for 30 min and a solution of tryptophol **11**[17] (0.52 g, 1.73 mmol) in THF (10 mL) was added dropwise. The reaction mixture was allowed to warm to −50 °C (1 h) and CuCN (196 mg, 2.19 mmol) was added. The reaction mixture was allowed to warm to rt and then was cooled again to −78 °C. Allyl bromide (0.17 mL, 1.96 mmol) was added, the reaction mixture was allowed to warm to rt, and the stirring was continued at rt for 12 h. The reaction mixture was diluted with 20% NH_4OH and extracted with CH_2Cl_2. The organic extracts were dried and concentrated and the resulting residue was chromatographed (from hexanes to 7:3 hexanes/AcOEt) to give the title compound **12** as an oil: 383 mg (65%); ^1H NMR (400 MHz) δ 2.92 (t, J=6.8 Hz, 2H), 3.78 (t, J=6.8 Hz, 2H), 3.85 (dt, J=6 and 1.6 Hz, 2H), 4.99–5.07 (m, 2H), 6.04 (ddt, J=17.2, 10.4, and 6 Hz, 1H), 7.26 (td, J=7.6 and 0.8 Hz, 1H), 7.32 (ddd, J=8, 7.6, and 1.6 Hz, 1H), 7.39 (td, J=7.2 and 1.6 Hz, 2H), 7.46–7.53 (m, 2H), 7.74 (dd, J=7.2 and 1.6 Hz, 2H), 8.21 (d, J=7.6 Hz, 1H); ^{13}C NMR (100.5 MHz) δ 27.7 (CH_2), 30.1 (CH_2), 61.8 (CH_2), 115.1 (CH), 116.0 (CH_2), 118.4 (C), 118.6 (CH), 123.5 (CH), 124.4 (CH), 126.2 (2 CH), 129.0 (2 CH), 130.3 (C), 133.5 (CH), 135.5 (CH), 135.6 (C), 136.5 (C), 138.7 (C); ESI-HRMS $[M+H]^+$ calcd for $C_{19}H_{20}NO_3S$ 342.1158, found 342.1159.

*4.3.2. Tosylate **13**.* *p*-Toluenesulfonyl chloride (0.63 g, 3.3 mmol), triethylamine (1.1 mL, 7.89 mmol), and DMAP (catalytic amount) were added to a solution of tryptophol **12** (1.02 g, 2.99 mmol) in CH_2Cl_2 (20 mL), and the resulting mixture was stirred at rt overnight. The reaction mixture was diluted with CH_2Cl_2 and successively washed with 1 N HCl and a saturated aqueous $NaHCO_3$ solution. The organic layer was dried and concentrated and the resulting residue was chromatographed (from hexanes to 4:1 hexanes/AcOEt) to give tosylate **13** as an oil: 1.33 g (90%); ^1H NMR (400 MHz) δ 2.38 (s, 3H), 2.98 (t, J=6.8 Hz, 2H), 3.75 (d, J=6 Hz, 2H), 4.12 (t, J=6.8 Hz, 2H), 4.91 (dd, J=17.2 and 1.2 Hz, 1H), 4.96 (dd, J=10 and 1.2 Hz, 1H), 5.89 (ddt, J=17.2, 10, and 6 Hz, 1H), 7.13 (d, J=7.6 Hz, 2H), 7.18 (t, J=7.6 Hz, 1H), 7.25–7.30 (m, 2H), 7.35–7.40 (m, 2H), 7.46–7.51 (m, 3H), 7.72 (d, J=7.6 Hz, 2H), 8.14 (d, J=7.6 Hz, 1H); ^{13}C NMR (100.5 MHz) δ 21.4 (CH_3), 24.1 (CH_2), 29.9 (CH_2), 68.5 (CH_2), 114.8 (CH), 116.0 (C), 116.1 (CH_2), 118.1 (CH), 123.4 (CH), 124.3 (CH), 126.2 (2 CH), 127.4 (2 CH), 129.1 (2 CH), 129.5 (2 CH), 132.2 (C), 133.6 (CH), 134.9 (CH), 135.9 (C), 136.2 (C), 138.7 (C), 144.6 (C), one quaternary C was not observed; ESI-HRMS $[M+NH_4]^+$ calcd for $C_{26}H_{29}N_2O_5S_2$ 513.1512, found 513.1507; ESI-HRMS $[M+Na]^+$ calcd for $C_{26}H_{25}NNaO_5S_2$ 518.1066, found 518.1060.

*4.3.3. 2-Allyl-3-[2-(N-allyl-N-tert-butoxycarbonylamino)ethyl]-1-(phenylsulfonyl)indole (**14**).* A mixture of tosylate **13** (0.71 g, 1.43 mmol), allylamine (0.8 mL, 10.7 mmol), K_2CO_3 (395 mg, 2.86 mmol), and a catalytic amount of LiI in CH_3CN (35 mL) was stirred at 85 °C in a sealed tube for 48 h. The reaction mixture was concentrated and the resulting residue was diluted with CH_2Cl_2 and washed with a saturated aqueous Na_2CO_3 solution. The organic layer was dried and concentrated to give the crude secondary amine (540 mg). A solution of the above amine, triethylamine (0.7 mL, 5.0 mmol), and (t-BuOCO)$_2$O (530 mg, 2.43 mmol) in MeOH (18 mL) was heated at reflux for 5 h. The solvent was removed and the residue was diluted with CH_2Cl_2 and washed with 2 N HCl and brine. The organic extracts were dried and concentrated to give the crude product. After column chromatography (from hexanes to 4:1 hexanes/AcOEt), diene **14** was obtained as an oil: 516 mg (75%); ^1H NMR (400 MHz, mixture of rotamers) δ 1.48 (s, 9H), 2.86 (br, 2H), 3.28 (br, 2H), 3.46 (br, 1H), 3.69 (br, 1H), 3.80 (d, J=6 Hz, 2H), 4.90–5.15 (m, 4H), 5.65 (br, 1H), 6.00 (m, 1H), 7.22–7.32 (m, 2H), 7.35–7.40 (m, 2H), 7.45–7.52 (m, 2H), 7.72 (d, J=8 Hz, 2H), 8.19 (d, J=7.6 Hz, 1H); ^{13}C NMR (100.5 MHz, mixture of rotamers) δ 23.0 (CH_2), 23.6 (CH_2), 28.4 (CH_3), 30.0 (CH_2), 46.1 (CH_2), 46.7 (CH_2), 49.8 (CH_2), 50.8 (CH_2), 79.5 (C), 79.8 (C), 115.1 (CH), 116.1 (CH_2), 116.7 (CH_2), 118.4 (CH), 118.7 (CH), 119.1 (C), 119.5 (C), 123.5 (CH), 124.4 (CH), 126.2 (2 CH), 129.0 (2 CH), 130.3 (C), 133.5 (CH), 134.1 (CH), 135.1 (C), 135.3 (CH), 136.5 (C), 138.9 (C), 155.1 (C); ESI-HRMS $[M+H]^+$ calcd for $C_{27}H_{33}N_2O_4S$ 481.2181, found 481.2182.

*4.3.4. 3-(tert-Butoxycarbonyl)-8-(phenylsulfonyl)-2,3,4,7-tetrahydro-1(H)-azonino[5,4-b]indole (**15**).* The second-generation Grubbs catalyst (30 mg, 0.035 mmol) was added under Ar to a solution of diene **14** (240 mg, 0.5 mmol) in CH_2Cl_2 (30 mL) and the resulting mixture was heated at reflux for 2 h 30 min. The reaction mixture was concentrated and the residue was purified by column chromatography (from hexanes to 4:1 hexanes/AcOEt) to give tricyclic carbamate **15** as a white foam: 170 mg (75%); ^1H NMR (400 MHz, mixture of rotamers) δ 1.28 and 1.44 (2s, 9H), 2.97 (m, 2H), 3.37–3.47 (m, 3.1H), 3.55 (m, 0.9H), 3.77 (d, J=6.8 Hz, 2H), 5.56 (dt, J=11.6 and 4.8 Hz, 0.55H), 5.73 (dt, J=11.2 and 4.8 Hz, 0.45H), 6.09 (m, 1H), 7.21–7.30 (m, 2H), 7.33–7.42 (m, 3H), 7.47 (t, J=7.6 Hz, 1H), 7.71 (m, 2H), 8.10 (m, 1H); ^{13}C NMR (100.5 MHz, mixture of rotamers) δ 23.8 (CH_2), 23.9 (CH_2), 24.1 (CH_2), 24.2 (CH_2), 28.2 (CH_3), 28.4 (CH_3), 43.3 (CH_2), 47.4 (CH_2), 48.2 (CH_2), 48.3 (CH_2), 79.5 (C), 79.7 (C), 114.9 (CH), 115.0 (CH), 117.6 (C), 118.1 (CH), 118.2 (CH), 118.9 (C), 123.3 (CH), 123.5 (CH), 124.3 (CH), 124.5 (CH), 126.2 (2 CH), 126.3 (2 CH), 127.7 (CH), 128.6 (CH), 129.0 (2 CH), 129.05 (2 CH), 129.1 (CH), 129.7 (CH), 133.4 (CH), 133.5 (CH), 134.7 (C), 136.1 (C), 136.4 (C), 136.6 (C), 138.9 (C), 139.1 (C), 154.9 (C), 155.7 (C); ESI-HRMS $[M+Na]^+$ calcd for $C_{25}H_{28}N_2NaO_4S$ 475.1662, found 475.1664.

*4.3.5. 3-(tert-Butoxycarbonyl)-2,3,4,7-tetrahydro-1(H)-azonino[5,4-b]indole (**16**).* Mg (230 mg, 9.46 mmol) was added to a solution of carbamate **15** (425 mg, 0.94 mmol) in MeOH (37 mL) cooled to 0 °C. After being stirred at rt for 4 h, the reaction mixture was poured into H_2O (80 mL). Warm CH_2Cl_2 (200 mL) was added and the mixture was gently stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to give the title compound **16**: 248 mg (84%); ^1H NMR (400 MHz, mixture of rotamers) δ 1.29 and 1.45 (2 s, 9H), 3.05 (m, 2H), 3.42 (m, 3H), 3.49 (m, 2H), 3.69 (d, J=4.4 Hz, 1H), 5.58 (m, 0.5H), 5.72 (m, 0.5H), 5.84 (m, 1H), 7.05–7.14 (m, 2H), 7.25 (d, J=7.6 Hz, 1H), 7.48 (m, 1H), 7.81 and 7.85 (2 br s, 1H); ^{13}C NMR (100.5 MHz, mixture of rotamers) δ 23.3 (CH_2), 23.6 (CH_2), 24.5 (CH_2), 25.1 (CH_2), 28.2 (CH_3), 28.4 (CH_3), 47.2 (CH_2), 47.5 (CH_2), 49.7 (CH_2), 79.3 (C), 79.5 (C), 109.3 (C), 110.0 (C), 110.2 (CH), 110.3 (CH), 117.5 (CH), 117.8 (CH), 118.9 (CH), 119.0 (CH), 121.1 (CH), 121.2 (CH), 126.0 (CH), 126.1 (CH), 127.5 (C), 128.2 (C), 129.9 (CH), 130.7 (CH), 132.6 (C), 132.9 (C), 135.3 (C), 135.6

(C), 155.3 (C), 155.9 (C); ESI-HRMS $[M+H]^+$ calcd for $C_{19}H_{25}N_2O_2$ 313.1911, found 313.1910.

*4.3.6. 3-[(Z)-2-Ethyl-3-iodo-2-propenyl]-8-(phenylsulfonyl)-2,3,4,7-tetrahydro-1(H)-azonino[5,4-b]indole (**17**).* A solution of carbamate **15** (243 mg, 0.54 mmol) in 1.2 M HCl in MeOH (25 mL) was stirred at rt for 5 h. The reaction mixture was basified with 20% NH_4OH and concentrated. The residue was partitioned between CH_2Cl_2 and H_2O and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give the crude secondary amine (182 mg). This material was allowed to react with diisopropylethylamine (0.14 mL, 0.80 mmol) and iodoalkene **4**[16] (145 mg, 0.53 mmol) in 1:1 CH_2Cl_2/acetonitrile (10 mL) as described for the preparation of **5**. After workup and column chromatography (from hexanes to 9:1 hexanes/AcOEt) the title compound **17** was obtained as an oil: 233 mg (79%); ^1H NMR (400 MHz) δ 0.74 (t, J=7.2 Hz, 3H), 1.88 (q, J=7.2 Hz, 2H), 2.70 (t, J=5.6 Hz, 2H), 2.91 (t, J=5.6 Hz, 2H), 3.10 (d, J=6.4 Hz, 2H), 3.20 (s, 2H), 4.01 (d, J=8 Hz, 2H), 5.65 (dt, J=10.8 and 6.4 Hz, 1H), 5.89 (s, 1H), 6.05 (dt, J=10.8 and 8 Hz, 1H), 7.18–7.27 (m, 2H), 7.34–7.41 (m, 3H), 7.50 (m, 1H), 7.75 (m, 2H), 8.13 (m, 1H); ^{13}C NMR (100.5 MHz) δ 11.9 (CH_3), 22.4 (CH_2), 24.8 (CH_2), 29.0 (CH_2), 49.8 (CH_2), 52.3 (CH_2), 61.9 (CH_2), 76.0 (CH), 114.8 (CH), 118.1 (CH), 120.4 (C), 123.2 (CH), 124.1 (CH), 126.2 (2 CH), 129.1 (2 CH), 129.2 (CH), 130.3 (C), 130.7 (CH), 133.4 (CH), 135.1 (C), 136.2 (C), 139.3 (C), 150.8 (C); ESI-HRMS $[M+H]^+$ calcd for $C_{25}H_{28}IN_2O_2S$ 547.0911, found 547.0909.

*4.3.7. 3-[(Z)-2-Ethyl-3-iodo-2-propenyl]-2,3,4,7-tetrahydro-1(H)-azonino[5,4-b]indole (**18**).* A solution of carbamate **16** (248 mg, 0.79 mmol) in 1.2 M HCl in MeOH (10 mL) was stirred at rt for 12 h. The reaction mixture was basified with 20% NH_4OH and concentrated. The residue was partitioned between CH_2Cl_2 and H_2O and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give the crude secondary amine (151 mg). This material was allowed to react with diisopropylethylamine (0.2 mL, 1.15 mmol) and iodoalkene **4**[16] (240 mg, 0.87 mmol) 1:1 CH_2Cl_2/acetonitrile (15 mL) as described above. After workup and column chromatography (from hexanes to 4:1 hexanes/AcOEt) amine **18** was obtained as an oil: 142 mg (44%); ^1H NMR (400 MHz) δ 0.93 (t, J=7.2 Hz, 3H), 2.14 (qd, J=7.2 and 0.8 Hz, 2H), 2.70 (t, J=5.6 Hz, 2H), 2.98 (t, J=5.6 Hz, 2H), 3.16 (d, J=5.6 Hz, 2H), 3.23 (s, 2H), 3.80 (d, J=8 Hz, 2H), 5.63 (m, 1H), 5.75 (m, 1H), 5.98 (s, 1H), 7.03–7.12 (m, 2H), 7.25 (dd, J=7.6 and 1.6 Hz, 1H), 7.46 (dd, J=7.6 and 1.2 Hz, 1H), 7.69 (br s, 1H); ^{13}C NMR (100.5 MHz) δ 12.3 (CH_3), 22.1 (CH_2), 26.9 (CH_2), 29.3 (CH_2), 52.5 (CH_2), 55.2 (CH_2), 62.5 (CH_2), 76.3 (CH), 110.1 (CH), 111.9 (C), 117.5 (CH), 118.9 (CH), 120.8 (CH), 127.4 (CH), 129.0 (C), 129.5 (CH), 132.6 (C), 134.5 (C), 150.6 (C); ESI-HRMS $[M+H]^+$ calcd for $C_{19}H_{24}IN_2$ 407.0979, found 407.0976.

*4.3.8. 8-(Phenylsulfonyl)-2,3,4,7-tetrahydro-1(H)-3,5-([2′]ethylprop[2′]eno)azonino[5,4-b]indole (**19**).* $Pd_2(dba)_3$ (28 mg, 0.03 mmol), xantphos (35 mg, 0.06 mmol), and K_2CO_3 (125 mg, 0.9 mmol) were added under Ar to a solution of vinyl iodide **17** (333 mg, 0.61 mmol) in 1:1 toluene/Et_3N (50 mL) and the resulting mixture was heated at 80 °C for 1 h 30 min. The solvent was removed and the residue was partitioned between CH_2Cl_2 and a saturated aqueous $NaHCO_3$ solution. The organic layer was dried and concentrated and the resulting residue was purified by column chromatography (from CH_2Cl_2 to 95:5 CH_2Cl_2/MeOH) to give tetracycle **19** as an oil: 217 mg (85%); ^1H NMR (500 MHz, assignment aided by $^1H-^1H$ COSY and HSQC) δ 0.98 (t, J=7.5 Hz, 3H, 18-H), 2.00 (m, 2H, 19-H), 2.72 (ddd, J=15.5, 11, and 4 Hz, 1H, 6-H), 2.91 (dt, J=15 and 3.5 Hz, 1H, 5-H), 3.10 (dt, J=15.5 and 3.5 Hz, 1H, 6-H), 3.16 (d, J=18 Hz, 1H, 21-H), 3.17 (d, J=11.5 Hz, 1H, 3-H), 3.26 (d, J=11.5 Hz, 1H, 3-H), 3.53 (ddd, J=15, 11, and 3.5 Hz, 1H, 5-H), 3.75 (dd, J=15.5 and 11 Hz, 1H, 16-H), 3.78 (d, J=18 Hz, 1H, 21-H), 4.04 (dd, J=15.5 and 4 Hz, 1H, 16-H), 5.41 (dd, J=11 and 4 Hz, 1H, 17-H), 6.32 (s, 1H, 15-H), 7.20 (ddd, J=7.5, 6.5, and 1 Hz, 1H, 10-H), 7.24 (dm, J=7.5 Hz, 1H, 9-H), 7.26 (ddd, J=8.5, 6.5, and 1 Hz, 1H, 11-H), 7.43 (m, 2H), 7.54 (tt, J=7.5 and 1.5 Hz, 1H), 7.75 (m, 2H), 8.21 (dt, J=8.5 and 1 Hz, 1H, 12-H); ^{13}C NMR (125.7 MHz, assignment aided by HSQC and HMBC) δ 12.2 (CH_3, C-18), 22.1 (CH_2, C-6), 26.8 (CH_2, C-19), 27.4 (CH_2, C-16), 55.2 (CH_2, C-21), 56.2 (CH_2, C-5), 58.7 (CH_2, C-3), 115.2 (CH, C-12), 117.9 (CH, C-9), 122.3 (CH, C-15), 123.4 (CH, C-10), 124.2 (CH, C-11), 126.3 (2 CH), 126.5 (C, C-7), 127.2 (CH, C-17), 129.2 (2 CH), 131.4 (C, C-8), 133.6 (CH), 136.5 (C, C-13), 137.0 (C, C-14), 139.1 (C, C-2), 139.3 (C), 142.1 (C, C-20); ESI-HRMS $[M+H]^+$ calcd for $C_{25}H_{27}N_2O_2S$ 419.1788, found 419.1785.

*4.3.9. 2,3,4,7-Tetrahydro-1(H)-3,5-([2′]ethylprop[2′]eno)azonino[5,4-b]indole (**20**). From vinyl iodide **18**.* Operating as above, from vinyl iodide **18** (90 mg, 0.22 mmol), tetracycle **20** was obtained after column chromatography (from Et_2O to 98:2 Et_2O/diethylamine): 46 mg (75%).

*From tetracycle **19**.* Mg (37 mg, 1.52 mmol) was added to a solution of **19** (105 mg, 0.25 mmol) in MeOH (10 mL) and the resulting mixture was stirred at rt for 4 h. Mg (34 mg, 1.40 mmol) was added again and the stirring was continued at rt for 1 h. Workup as described for the preparation of **16** and column chromatography (from Et_2O to 98:2 Et_2O/diethylamine) gave the title compound **20** as an oil: 62 mg (88%); ^1H NMR (400 MHz) δ 1.14 (t, J=7.2 Hz, 3H), 2.15 (q, J=7.2 Hz, 2H), 2.69 (ddd, J=15.6, 10.8, and 3.2 Hz, 1H), 2.79 (dt, J=14.8 and 3.2 Hz, 1H), 3.06 (dd, J=14 and 3.6 Hz, 1H), 3.16 (d, J=12.4 Hz, 1H), 3.22 (dt, J=15.6 and 3.2 Hz, 1H), 3.30 (d, J=18.4 Hz, 1H), 3.34 (d, J=12.4 Hz, 1H), 3.66 (ddd, J=14.8, 10.8, and 3.2 Hz, 1H), 3.84 (d, J=18.4 Hz, 1H), 3.89 (dd, J=14 and 11.6 Hz, 1H), 5.61 (dd, J=11.6 and 3.6 Hz, 1H), 6.52 (s, 1H), 7.02–7.11 (m, 2H), 7.24 (d, J=7.2 Hz, 1H), 7.36 (dd, J=7.2 and 1.2 Hz, 1H), 7.96 (br, 1H); ^{13}C NMR (100.5 MHz) δ 12.3 (CH_3), 20.6 (CH_2), 26.9 (CH_2), 29.4 (CH_2), 54.4 (CH_2), 57.2 (CH_2), 59.7 (CH_2), 110.3 (CH), 116.5 (C), 117.4 (CH), 119.2 (CH), 120.9 (CH), 122.7 (CH), 125.7 (CH), 130.0 (C), 134.3 (C), 136.1 (C), 136.3 (C), 141.8 (C); ESI-HRMS $[M+H]^+$ calcd for $C_{19}H_{23}N_2$ 279.1856, found 279.1856.

*4.3.10. NMR data of tetracycle **21**·HCl.* ^1H NMR (400 MHz) δ 1.03 (t, J=7.2 Hz, 3H), 2.01 (m, 2H), 2.74 (m, 1H), 2.84 (br s, 1H), 3.04 (dt, J=18.4 and 3 Hz, 1H), 3.21 (d, J=16.8 Hz, 1H), 3.50 (m, 2H), 3.72 (d, J=13.2 Hz, 1H), 3.94 (d, J=16.8 Hz, 1H), 4.05 (m, 1H), 4.25 (m, 1H), 5.61 (s, 1H), 5.84 (d, J=12.8 Hz, 1H), 6.82 (d, J=12.8 Hz, 1H), 7.30–7.66 (m, 8H), 8.29 (d, J=8.4 Hz, 1H).

*4.3.11. NMR data of tetracycle **22**.* ^1H NMR (400 MHz, assignment aided by $^1H-^1H$ COSY and HSQC) δ 0.91 (dd, J=14.4 and 9.2 Hz, 1H, 6-H), 1.11 (t, J=7.6 Hz, 3H, 18-H), 1.84 (d, J=14 Hz, 1H, 3-H), 2.28 (m, 2H, 19-H), 2.84 (d, J=14 Hz, 1H, 3-H), 3.05 (dd, J=14.4 and 7.2 Hz, 1H, 6-H), 3.15 (dd, J=13.2 and 9.2 Hz, 1H, 5-H), 3.53 (dd, J=13.2 and 7.2 Hz, 1H, 5-H), 6.28 (s, 1H, 21-H), 6.32 (s, 1H, 15-H), 6.79 (d, J=12 Hz, 1H, 16-H), 6.90 (d, J=12 Hz, 1H, 17-H), 7.24–7.32 (m, 4H), 7.34–7.42 (m, 2H), 7.68 (dd, J=7.5 and 1.2 Hz, 2H), 8.34 (d, J=8.4 Hz, 1H, 12-H); ^{13}C NMR (100.5 MHz, assignment aided by HSQC and HMBC) δ 15.4 (CH_3, C-18), 25.5 (CH_2, C-19), 27.7 (CH_2, C-6), 42.8 (CH_2, C-3), 57.1 (CH_2, C-5), 110.7 (CH, C-16), 113.9 (C, C-14), 116.2 (CH, C-12), 118.1 (CH), 123.6 (C, C-20), 124.0 (C, C-7), 124.1 (CH), 125.1 (CH), 126.7 (2 CH), 128.7 (2 CH), 131.0 (C, C-8), 131.9 (CH, C-15), 133.1 (CH, C-21), 133.4 (C, C-2), 133.6 (CH), 134.2 (CH, C-17), 137.3 (C, C-13), 138.6 (C); ESI-HRMS $[M+H]^+$ calcd for $C_{25}H_{25}N_2O_2S$ 417.1631, found 417.1624.

*4.3.12. Catalytic hydrogenation of **20**. Method A.* Diene **20** (43 mg, 0.15 mmol) dissolved in AcOEt (2.5 mL) was hydrogenated over PtO_2 (7 mg, 0.03 mmol) at rt for 1 h. The reaction mixture was filtered through Celite, washing carefully with warm MeOH. The

filtrate was concentrated and the resulting residue was purified by column chromatography (Al_2O_3, from hexanes to 1:1 hexanes/CH_2Cl_2) to give (±)-cleavamine[20] (**23**, 17 mg, 40%) and (±)-dihydrocleavamine[21] **24** (10 mg, 23%). *(±)-Cleavamine* (**23**): ^{1}H NMR (400 MHz, assignment aided by HSQC) δ 1.07 (t, J=7.4 Hz, 3H, 18-H), 1.90–2.01 (m, 2H, 17-H), 2.04 (q, J=7.4 Hz, 2H, 19-H), 2.11 (br, 1H, 14-H), 2.34–2.44 (m, 2H, 3-H and 5-H), 2.45 (m, 1H, 5-H), 2.60 (ddd, J=13.4, 7, and 0.8 Hz, 1H, 16-H), 2.69–2.79 (m, 2H, 3-H and 6-H), 2.80 (m, 1H, 6-H), 3.06 (d, J=15.6 Hz, 1H, 21-H), 3.16 (d, J=15.6 Hz, 1H, 21-H), 3.73 (dd, J=13.4 and 12.4 Hz, 1H, 16-H), 5.29 (d, J=4 Hz, 1H, 15-H), 7.04–7.13 (m, 2H, 10-H and 11-H), 7.28 (dm, J=7.2 Hz, 1H, 12-H), 7.48 (dd, J=7.2 and 1.6 Hz, 1H, 9-H), 7.78 (br, 1H, NH); ^{13}C NMR (125.7 MHz, assignment aided by HSQC) δ 12.6 (CH_3, C-18), 22.5 (CH_2, C-16), 26.1 (CH_2, C-6), 27.6 (CH_2, C-19), 34.1 (CH_2, C-17), 35.3 (CH, C-14), 53.5 (CH_2, C-3), 53.9 (CH_2, C-5), 55.1 (CH_2, C-21), 109.8 (CH, C-12), 109.9 (C, C-7), 117.8 (CH, C-9), 118.7 (CH, C-10), 120.6 (CH, C-11), 122.4 (CH, C-15), 128.7 (C, C-8), 135.4 (C, C-13), 139.4 (C, C-2), 140.8 (C, C-20); ESI-HRMS $[M+H]^+$ calcd for $C_{19}H_{25}N_2$ 281.2012, found 281.2016. *(±)-Dihydrocleavamine* (**24**): ^{1}H NMR (400 MHz) δ 0.88 (t, J=7.6 Hz, 3H), 1.31 (m, 2H), 1.41–1.63 (m, 3H), 1.75 (m, 2H), 1.91 (dddd, J=12.4, 11.6, 6.4, and 1.2 Hz, 1H), 2.17 (dd, J=12 and 6 Hz, 1H), 2.26 (d, J=12 Hz, 1H), 2.33 (m, 1H), 2.40–2.52 (m, 2H), 2.62 (d, J=7.2 Hz, 1H), 2.65 (d, J=7.2 Hz, 1H), 2.82–2.88 (m, 2H), 3.70 (t, J=12.8 Hz, 1H), 7.04–7.12 (m, 2H), 7.28 (dd, J=8 and 1.2 Hz, 1H), 7.46 (dd, J=8 and 1.2 Hz, 1H), 7.78 (br, 1H); ^{13}C NMR (125.7 MHz) δ 11.7 (CH_3), 21.1 (CH_2), 26.3 (CH_2), 28.7 (CH_2), 31.2 (CH_2), 32.7 (CH), 33.7 (CH_2), 35.1 (CH), 51.7 (CH_2), 52.2 (CH_2), 59.0 (CH_2), 109.9 (CH), 110.1 (C), 117.8 (CH), 118.8 (CH), 120.6 (CH), 128.5 (C), 135.5 (C), 138.8 (C); ESI-HRMS $[M+H]^+$ calcd for $C_{19}H_{27}N_2$ 283.2169, found 283.2166.

Method B. Diene **20** (62 mg, 0.22 mmol) in AcOEt (3.5 mL) was hydrogenated over PtO_2 (13 mg, 0.057 mmol) at rt for 5 h. Workup and column chromatography as above gave **24**: 27 mg (43%).

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Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra of all new compounds. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.01.064.

References and notes

1. For general reviews, see: (a) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 2; (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238.
2. For general reviews, see: (a) Bräse, S.; de Meijere, A. In *Metal-catalyzed Cross-coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, NY, 2004; pp 217–316; (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644–4680.
3. (a) Bennasar, M.-L.; Zulaica, E.; Solé, D.; Alonso, S. *Synlett* **2008**, 667–670; (b) Bennasar, M.-L.; Zulaica, E.; Solé, D.; Alonso, S. *Tetrahedron* **2012**, *68*, 4641–4648.
4. (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.
5. (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) Martin, D. B. C.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 3472–3473.
6. (a) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685–2686; (b) Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidró, E.; Bosch, J. *Chem.—Eur. J.* **2000**, *6*, 655–665; (c) 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; (d) Mori, M.; Nakanishi, M.; Kahishima, D.; Sato, Y. *J. Am. Chem. Soc.* **2003**, *125*, 9801–9807; (e) Martin, D. B. C.; Nguyen, L. Q.; Vanderwal, C. D. *J. Org. Chem.* **2012**, *77*, 17–46.
7. Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2008**, *130*, 5368–5377.
8. For reviews, see: (a) Cordell, G. A. In *Indoles, The Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; Wiley: New York, NY, 1983; Vol. 25, Part 4, Chapter 10; (b) Saxton, J. E. In *Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; Wiley: Chichester, UK, 1994; Supplement to Vol. 25, Part 4, Chapter 10.
9. Sundberg, R. J.; Smith, S. Q. In *The Alkaloids*; Cordell, G. A., Ed.; Academics: Amsterdam, The Netherlands, 2002; Vol. 59, Chapter 2.
10. *The Alkaloids*; Brossi, A., Ed.Suffness, M., Ed.; Academic: San Diego, CA, 1990; Vol. 37.
11. Mangeney, P.; Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P. *J. Org. Chem.* **1979**, *44*, 3765–3768.
12. For reviews on the synthesis of medium-sized rings by RCM, see: (a) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073–2077; (b) Yet, L. *Chem. Rev.* **2000**, *100*, 2963–3007; (c) Michaut, A.; Rodriguez, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 5740–5750.
13. For example, see: (a) Grigg, R.; Sridharan, V.; York, M. *Tetrahedron Lett.* **1998**, *39*, 4139–4142; (b) Enders, D.; Lenzen, A.; Backes, M.; Janeck, C.; Catlin, K.; Lannou, M.-I.; Runsink, J.; Raabe, G. *J. Org. Chem.* **2005**, *70*, 10538–10551; (c) 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.
14. For a preliminary communication of part of this work, see: Bennasar, M.-L.; Solé, D.; Zulaica, E.; Alonso, S. *Org. Lett.* **2011**, *13*, 2042–2045.
15. Bennasar, M.-L.; Zulaica, E.; Solé, D.; Alonso, S. *Tetrahedron* **2007**, *63*, 861–866.
16. Zhang, Y.; Herndon, J. W. *Org. Lett.* **2003**, *5*, 2043–2045.
17. Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Leahy, E. M.; Salvino, J.; Arison, B.; Cichy, M. A.; Spoors, P. G.; Shakespeare, W. C.; Sprengeler, P. A.; Hamley, P.; Smith, A. B., III; Reisine, T.; Raynor, K.; Maechler, L.; Donaldson, C.; Vale, W.; Freidinger, R. M.; Cascieri, M. R.; Strader, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 12550–12568.
18. For examples in the literature, see: (a) Clark, J. S.; Marlin, F.; Nay, B.; Wilson, C. *Org. Lett.* **2003**, *5*, 89–92; (b) Schwartz, K. D.; White, J. D. *Org. Lett.* **2011**, *13*, 248–251.
19. The structure of **21** could be determined by ^{1}H NMR analysis of the corresponding hydrochloride.
20. For NMR data of cleavamine, see: (a) Kutney, J. P.; Brown, R.; Piers, E. *Can. J. Chem.* **1965**, *43*, 1545–1552; (b) Imanishi, T.; Nakai, A.; Yagi, N.; Hanaoka, M. *Chem. Pharm. Bull.* **1981**, *29*, 901–903; (c) Wenkert, E.; Hagaman, E. W.; Kunesch, N.; Wang, N.-Y. *Helv. Chim. Acta* **1976**, *59*, 2711–2723.
21. For NMR data of (+)-20*R*-dihydrocleavamine, see: van Beek, T. A.; Verpoorte, R.; Svendsen, A. B. *Tetrahedron* **1984**, *40*, 737–748.