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An Efficient Synthesis of a Fully Functionalized 7-Aminoaziridinomitosene

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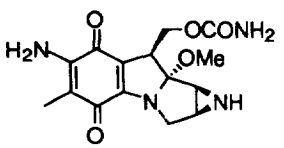
Abstract: An efficient approach for the synthesis of a fully functionalized 7-aminoaziridinomitosene has been developed. Commencing with the known 2,3,5,6,7,8-hexahydro-8-oxo-1*H*-pyrrolo[1,2-*a*]indole **6**, twelve transformations leads to the novel 7-aminoaziridinomitosene **4** in 11% overall yield. This study demonstrates the feasibility of installing the free aziridine and the aminoquinone functionalities on the pyrrolo[1,2-*a*]indole skeleton. © 1997 Elsevier Science Ltd.

INTRODUCTION

Synthetic efforts directed towards the pyrrolo[1,2-*a*]indole ring system is an major area of interest[1] due to presence of this structural subunit in the mitomycin and mitosene class of anticancer alkaloids. Notably, mitomycin C (**1**) is an important clinical drug which has been used extensively in cancer chemotherapy treatments. The 7-aminoleucoaziridinomitosene (**2**) is believed to be the key bioactive factor[2] which is derived from **1** via reductive activation. The oxidized relative of **2**, 7-aminoaziridinomitosene (**3**, X = NH_2) can be chemically derived[2] from mitomycin C, although it does not reveal significant anticancer activity unlike other 7-substituted aziridinomitosenes.[3] Considerable effort has been directed towards understanding the mode of action for mitomycin C and related agents and continues unabated.[4] In addition to the formidable challenges presented in the total synthesis of these targets, there remains a major interest in the synthesis and biological evaluation of structural analogues[5] which maintain high activity towards cancer cells and reveal lower associated toxicity towards healthy cells.



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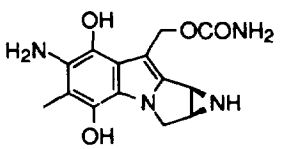

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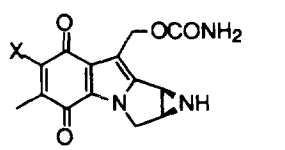
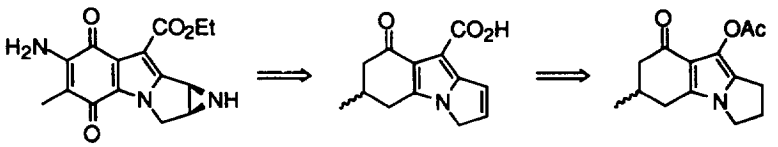


3

In recent years our program has been focused on the development of a simple pyrrole annulation approach for the synthesis of a variety of pyrrole containing heterocyclic systems.[6] In this report we reveal an efficient 12-step route to a fully functionalized aziridinomitosene analogue **4** commencing from the easily obtained

2,3,5,6,7,8-hexahydro-8-oxo-1*H*-pyrrolo[1,2-*a*]indole **6** and proceeding via the known unsaturated acid **5**.[7] Previously, Franck and co-workers[8] reported a highly efficient two-step route to compound **6** starting with commercially available 5-methyl-cyclohexane-1,3-dione and sodium prolinate. Since this time further efforts towards the mitosenes using these precursors have not been pursued.

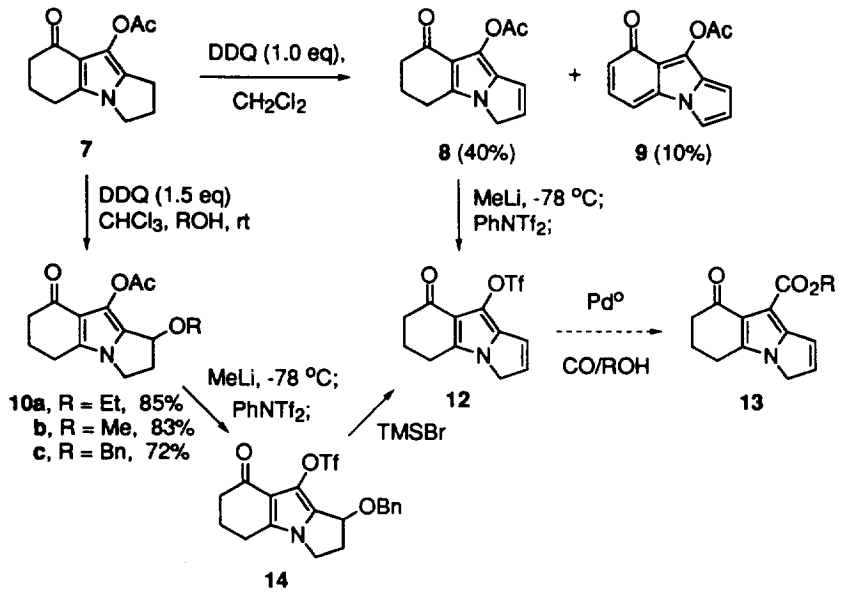


4 **5** **6**

BACKGROUND STUDIES

In the initial phases of this effort we needed to develop a means for introducing appropriate functionality in the C^1/C^2 positions from a unsubstituted precursor such as **6**, which, would eventually lead to an aziridine ring in the final target compound(s). In a preliminary report the regioselective oxidation of a model 2,3,5,6,7,8-hexahydro-8-oxo-1H-pyrrolo[1,2-a]indole **7** was determined.[6b] At first, exposure of **7** to DDQ in dry, alcohol free solvent afforded the C^1/C^2 unsaturated compound **8**, the over oxidized product **9**, and recovered starting material (Scheme 1). With some effort **8** could be isolated in around 40% yield by careful recrystallization of the crude reaction mixture from ethyl acetate/hexanes. Although this result showed initial promise, difficulties with isolating quantities of **8** rendered this approach impractical. Attempts to optimize this reaction by variation of solvent and reaction temperature fortuitously lead to the isolation of the C^1 substituted ether **10a** as a minor by-product. This was attributed to traces of ethanol present in the chloroform. By adding in several equivalents of various alcohols, good yields of the C^1 functionalized ethers **10a-c** could be realized. At this stage further conversion into the C^1 triflate derivative **12** was needed. Either of two approaches proved workable. From alkene **8**, exposure to MeLi at -78 °C followed by $PhNTf_2$, according to our protocol reported earlier,[6a] afforded a modest yield of **12**. An alternative path to this compound was realized by first treating C^1 benzyl ether **10c** with the same reaction conditions to give a new triflate **14**. Hoping to cleave the benzyl ether and generate a C^1 alcohol, treatment of **14** with TMSBr afforded instead, the unsaturated triflate **12** via direct elimination of benzyl alcohol. As a result, a more convenient route to this compound was uncovered. Unfortunately, attempts to effect the palladium-catalyzed alkoxy- or hydroxycarbonylation of **12**, using a variety of established procedures,[9] met with failure. Basically, no reaction was observed and attempts to force the reaction by heating or CO pressurization led to the precipitation of palladium black. At this stage the only remaining way to salvage our approach would have to rely upon a reordering of steps, i.e., carbonylation of C^1 substituted triflate **14** and then liberation of the C^1/C^2 alkene after the carboxy group was in place. Realizing our position and desiring to move into the actual system which would ultimately lead to authentic mitosene structures, we turned our attention to the C^5 methyl substituted system **6**.

Scheme 1

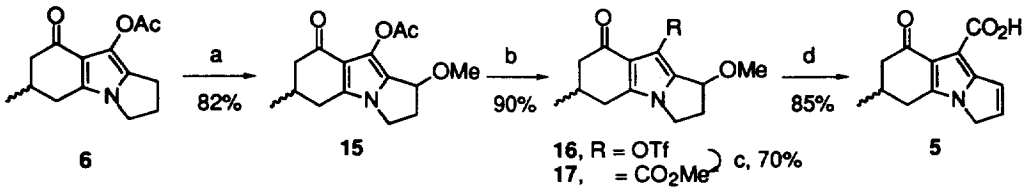


PREPARATION OF UNSATURATED ACID 5

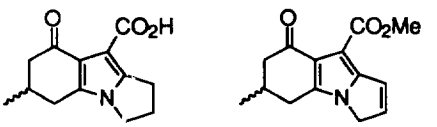
In an effort to take advantage of the new chemistry discovered in our model studies, an improved route to the known unsaturated acid **5** from Franck's compound **6** was deemed a worthy venture (Scheme 2). Thus, reaction of **6** with DDQ in the presence of methanol predictably afforded the C^1 methyl ether **15** in good yield. Subsequent conversion into the triflate **16** proceeded without incident. The palladium-catalyzed methoxycarbonylation of **16** proved troublesome at first. Under typical reaction conditions reported in the literature (Ph_3P:Pd^o, 4.5:1),[9a] palladium black precipitated within minutes after warming the reaction mixture, and the yield of desired ester **17** was low (< 20%). Using the bidendate ligand, dppp,[9b] afforded similar results. Fortunately, it was found that in order to preserve catalyst life a high ratio of phosphine ligand to palladium (7.2:1) was necessary. In this way, reasonable yields of **17** could be realized. The next transformation it was hoped that simultaneous cleavage of the methyl ester and elimination of methanol would occur and lead to the unsaturated acid **5**. Initial attempts using *in-situ* generated TMSI proved troublesome. Exposure of **17** to 2.1 equivalents of this reagent in acetonitrile at 50 °C for 4 h resulted in the formation of two new spots by TLC analysis. An ^1H NMR analysis of the crude reaction mixture indicated that the minor product of this reaction was the desired alkene **5**. The major product was later determined to be the reduction product **18**. Shortening the reaction time improved the yield of **5** towards 50% however, considerable quantities of the intermediate **19** remained. Since the reduction of the desired product appeared to be the consequence of excess iodide ion in solution, it was reasoned that use of trimethylsilyl bromide (TMSBr)[10] would avoid this undesired reaction. In practice, exposure of **6** to excess TMSBr provided the desired unsaturated acid **5** in good yield following aqueous workup. This compound proved identical in all respects with the material originally reported by Rebek.[7] The original route to **5** proceeded in 8 steps and 17% overall

yield from trans-4-hydroxy proline and 3-methylglutaric anhydride. By way of comparison, our route proceeds in 6 steps and 26% overall yield from sodium prolinate and 5-methylcyclohexane-1,3-dione.

Scheme 2



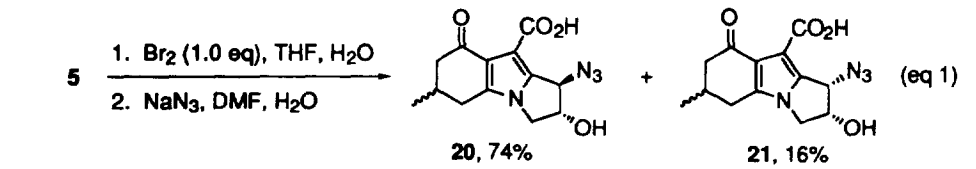
[a]Reagents: (a) DDQ (1.3 eq), CH_2Cl_2, MeOH, rt, 1 h;
(b) MeLi (2.0 eq), THF, -78 °C; $PhNTf_2$;
(c) $Pd(OAc)_2$/CO, MeOH, DMSO, Et_3N, 70 °C;
(d) TMSCl, LiBr, MeCN, 55 °C



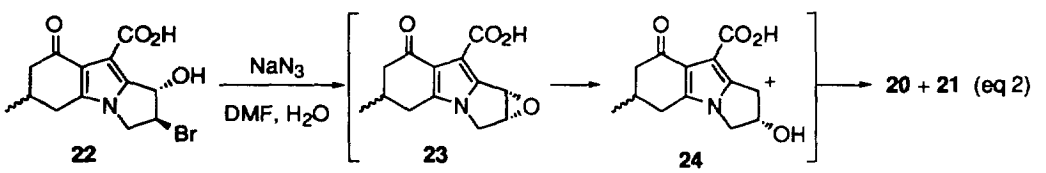
18 19

In Rebek's work compound **5** was used for the preparation of various C^1-C^2 disubstituted mitosene derivatives, however, attempts to make aziridinomitosene systems from this intermediate were not pursued.[7] Our interest then became whether this compound could be relayed into a fully functionalized 7-aminoaziridinomitosene, a task not proven in the literature. In fact, the only demonstrated fully synthetic route to these particular mitosenes was reported from the Rapoport group.[1d] Here, the final target obtained was a 7-methoxyaziridinomitosene bearing an C^9 ester group and a benzyl group on the aziridine nitrogen. More commonly, mitosene derivatives are derived semi-synthetically from naturally occurring mitomycins.[1h, 2] In pursuit of developing a fully synthetic route to aziridinomitosenes, we were able to take advantage of two key transformations developed by Rebek[7] to install the aminoquinone portion and the azidomesylate functionality at C^1 and C^2.

In our hands **5** was treated with aqueous bromine to afford a high yield of bromohydrin which, was directly treated with sodium azide in aqueous DMF to afford an easily separable mixture of the *trans*- and *cis*-azido alcohols, **20** and **21**, respectively (eq 1). Notably, Rebek only reported isolation of the *trans*-isomer in his study. The assignment of the minor isomer having *cis*-stereochemistry and relative regiochemistry, as shown for **21**, is based on the following ^1H NMR analysis. Two overlapping doublets for H-1 appeared in the range 5.36-5.38 ppm with an coupling to the adjacent H-2 proton of $J_{1,2}$ = 5.8 Hz. The signal for H-2 appeared as a broad multiplet centered at 4.87 ppm. In a subsequent deuterium exchange experiment the signal for H-2 simplified to a broadened five line pattern, from which, the two coupling constants were measured, $J_{1,2}$ = 5.7 Hz and $J_{2,3}$ = 7.2 Hz. The two overlapping peaks for H-1 remained unchanged. This confirmed the position of the OH group at C^2. The possibility for the *trans*-2-azido-1-hydroxy isomer being assigned to **21** was ruled out based on comparison of ^1H spectral data with authentic compounds prepared first, by Remers and Weiss,[11] and later by Rebek.[7] Furthermore, the ^1H NMR data for the *trans*-isomer **20**, and similar compounds,[7] reveals a coupling constant for $J_{1,2}$ near zero in all cases. Thus, the *cis*-configuration for **21** was assigned based on the constant for $J_{1,2}$ of 5.8 Hz.

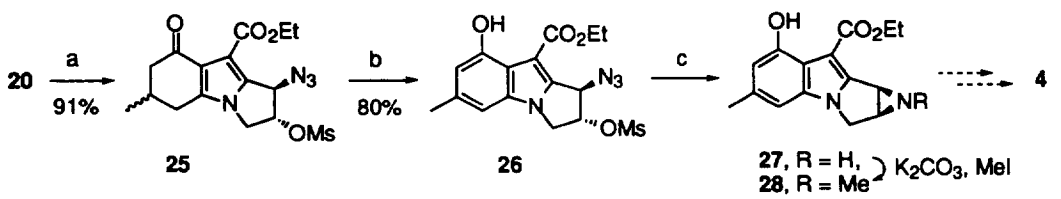


The stereochemical outcome of this transformation deserves special comment. Based on established mechanistic grounds, the likely intermediate in this process is the transient 1,2-epoxide, **23** (eq 2). Reaction with nucleophiles occurs exclusively at C^1 as a result of powerful electronic effects, as evidenced by the exclusive formation of 1-azidoadducts **20** and **21**. However, the resulting stereochemistry of the 1-substituted-2-hydroxy adducts depends greatly upon the reaction conditions. For example, Rebek reported that a *cis*-1-methoxy-2-hydroxy adduct was isolated as the major product when **22** was exposed to basic reaction conditions (NaOMe/MeOH).[7] In this case the product *cis/trans* ratio was found to be inversely proportional to the base concentration, a fact which, suggested that the minor *trans*-adduct arose directly via S_N2 attack on the epoxide **23**. To explain the formation of the *cis*-adduct, intervention of a short lived zwitterionic intermediate, **24**, evolving from a solvolysis reaction component, was proposed. Here the incipient alkoxide ion is protonated by a solvent molecule, i.e. MeOH, which then attacks the carbocation from the same side.



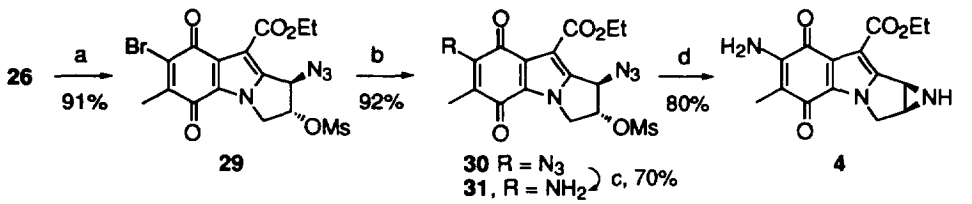
On the other hand, reaction of **22** with azide as the nucleophile presents a more difficult case to rationalize. Notably, we were able to isolate a minor amount of the *cis*-adduct **21** under the same conditions reported by Rebek. A likely explanation for their result is that the more polar *cis*-isomer was in fact formed, but was not eluted from the silica gel column during purification (hexanes/ethyl acetate as the eluant). In our hands column chromatography required elution of **21** using EtOAc/MeOH (9:1) compared with the more mobile *trans*-isomer which was eluted quickly using $CHCl_3$/EtOAc (1:1). To explain the reaction outcome, direct S_N2 attack of azide on the epoxide **23** would logically lead to the *trans*-adduct **20**. It would seem necessary however, to invoke the intermediacy of the zwitterion **24** to explain the formation of the *cis*-isomer. What is troubling is how such a species would form via a solvolysis process, in this case aqueous DMF, and not see the formation of secondary products, i.e. 1,2-diols. This suggests that intermediate **24** is sufficiently long lived to allow effective competition by azide for the C^1 carbocation. This brings up another plausible explanation that the entire reaction manifold proceeds via **24** and the subsequent stereochemical outcome is dictated by steric preferences alone. In this case the azide ion preferentially attacks C^1 opposite to the hydroxy group leading to *trans*-stereochemistry. These salient mechanistic details merit further investigation, especially in regard to solvent effects and the nature of the nucleophile. Similar peculiarities involving the stereochemistry for ring opening reactions of mitomycins and aziridinomitosenes are well known .[1b, 7]

Proceeding from the *trans*-azidoalcohol **20**, an improved, one-step method for the conversion into the C^9 ester-mesylate **25** was developed. Previously, Rebek converted the C^2 alcohol into its mesylate derivative, then esterified the C^9 carboxyl group using a time intensive alkylation reaction. Conveniently, we found that exposure of **20** to excess mesyl chloride presumably generated a transient acyl mesylate along with mesylation of the C^2 hydroxyl which, upon quenching the crude reaction mixture with ethanol, lead directly to the ethyl ester **25** in high yield. As expected, DDQ mediated dehydrogenation of **25** afforded the 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole **26**. At this stage we were eager to establish the aziridine ring and were pleased to demonstrate this task, via the agency of an iminophosphorane intermediate,[12] to afford compound **27**. However, further attempts to convert this material, or its *N*-methyl derivative **28**, into mitosenes, e.g. **4**, met with failure. Apparently the aziridine ring would not tolerate reaction conditions[13] required to elevate the oxidation state of the A-ring phenol into a quinone, complex reaction mixtures were typically observed.



(a) MsCl, Et_3N, THF; EtOH; (b) DDQ, EtOAc; (c) Ph_3P, Et_3N, THF, H_2O.

To realize the final end target, an aminoaziridinomitosene, it became apparent that the sensitive aziridine ring would have to be installed in the last step. Thus, solvolytic bromination of **26** according to Rebek's procedure[7] gave an instantaneous reaction which resulted in the high yield conversion into the bromoquinone **29**. The next challenge became the installation of the 7-amino group. Initially the method of Rebek was tried, i.e. exposure of **29** to excess sodium azide in hot DMF, however, only 25-40% yield of the desired aminoquinone **31** was afforded. Attempts to carry out direct amination of **29** by exposure to aminodiphenylmethane gave no reaction in acetonitrile, whereas in DMF, the reaction produced a deep colored polar material which could not be readily characterized. On the other hand, reaction of **29** with a slight excess of sodium azide in acetonitrile afforded a high yield of the 7-azidoquinone **30**. Attempts to selectively reduce the azido group in **30** by treatment with triphenylphosphine in the presence of water, gave numerous products as evidenced by TLC analysis. Fortunately, recourse to the long known path of thermal disproportionation of azidohydroquinones provided a satisfactory outcome.[14] In anticipation, exposure of **30** to sodium dithionite afforded a sensitive azidohydroquinone intermediate which, was used directly without isolation in the subsequent thermal reaction. After considerable experimentation, it was found that the desired 7-aminoquinone **31** could be obtained by refluxing the azidohydroquinone in chloroform for 8 hrs, removal of solvent, introduction of toluene and refluxing for another 4 hr period. In this way **31** could be isolated in 70% yield from **30**. Interestingly, if the azidohydroquinone was heated directly in toluene an unknown by-product appeared; this material was minimized with the chloroform preheating step. What appears to be happening is a stepwise disproportionation process which is facilitated in the desired direction by a two-stage heating process. Finally, the aziridine was readily introduced in the last step utilizing the method mentioned earlier to afford the 7-aminoaziridinomitosene **4** in 80% as a purple solid.[15]



(a) Br_2, THF, H_2O, AcOH, NaOAc; (b) NaN_3, CH_3CN, H_2O; (c) $Na_2S_2O_4$, EtOH; $CHCl_3$, Δ; $PhCH_3$, Δ; (d) Ph_3P, Et_3N, THF, H_2O.

CONCLUSION

An efficient and economical new approach towards the synthesis of 7-amino-aziridinomitosenes, as represented by compound **4**, has been developed in less than fifteen total operations from commercially available chemicals. Overall our scheme represents the second total synthesis of a fully functionalized aziridinomitosene. At one stage, new insights into the mechanistic details involving the reaction of 1,2-epoxypyrrolo[1,2-*a*]indoles with nucleophiles is provided. Notably, our route has the advantage of accessing both the aziridine and 7-amino substituents in deprotected form. Further application of this synthetic approach to additional C^9 substituted mitosenes will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Details: The following solvents and reagents were distilled from calcium hydride; dichloromethane, acetonitrile, 2,4,6-collidine, and triethylamine. THF was distilled from potassium metal under a nitrogen atmosphere. Unless otherwise noted, materials were obtained from commercially available sources and used without further purification. Sodium sulfate was used as a drying reagent in all cases. Melting points were recorded on a Thomas-Hoover apparatus and are uncorrected. IR spectra were determined with a Perkin Elmer 1750 spectrophotometer. ^1H NMR spectra were recorded at 270 MHz and 400 MHz with tetramethylsilane, $CDCl_3$ (7.25 ppm) or DMSO (2.49 ppm) used as the internal references. ^{13}C NMR were recorded at 67.9 MHz, $CDCl_3$ (77.0 ppm) or DMSO (39.5 ppm) were used as the internal references. The ^1H and ^{13}C spectral data for compounds **6**, **15**, **16**, **17**, **5**, **20**, **21**, and **25** are reported for the (1:1) mixture of diastereomers as a result of the random C^6 stereocenter. The ^{13}C data is reported in brackets for each doubled peak. Elemental analysis were performed by Atlantic Microlab, Inc.. High resolution mass spectra was performed by UCR Mass spec. facility, Department of Chemistry, University of California, Riverside. Column chromatography was performed with silica gel (Merck 60 Å, 230-400 mesh).

9-Acetoxy-1-methoxy-6-methyl-1,2,5,6,7,8-hexahydro-8-oxo-3*H*-pyrrolo[1,2-*a*]indole (15). To a solution of **6**[8] (1.10 g, 4.45 mmol) in 45 ml CH_2Cl_2 and 2 ml of MeOH was added DDQ (1.32 g, 5.81 mmol). The resulting dark solution was stirred at room temperature under an atmosphere of N_2 for 1 hour and 45 mins. The suspension was filtered, the mother liquid was diluted with $CHCl_3$ and washed with brine and water. The solvent was dried and removed under vacuum. The residue was chromatographed with EtOAc/hexanes (4:1) to

give 1.05 g (85%) **15** as a light yellow solid (this sample was used in the next reaction without further purification): mp 90.5-95.5 ^{0}C; IR ($CHCl_3$) 2954, 1779, 1658, 1594, 1473 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.56-4.57 and 4.58-4.60 (d, two overlapping sets of doublets, J = 5.9 Hz, 1 H), 3.72-3.94 (m, 2 H), 3.21 (s, 3 H), 2.03-2.71 (m, 7 H), 2.23 (s, 3 H), 1.18 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 192.3, 169.2, 136.2 (136.1), 127.9, 125.5 (125.5), 114.7, 74.1 (73.9), 55.8 (55.7), 46.2 (46.2), 42.7 (42.6), 35.8 (35.8), 31.2 (31.0), 29.78 (29.7), 21.0 (20.9), 20.4. HRMS (DCI, M + H$^+$) calcd for $C_{15}H_{19}NO_4$: 278.1392, found: 278.1402.

1-Methoxy-6-methyl-1,2,5,6,7,8-hexahydro-8-oxo-9-trifloromethanesulfonyl-3*H*-pyrrolo[1,2-*a*]indole (16). A solution of **15** (500 mg, 1.81 mmol) in 25 ml THF cooled at -78 ^{0}C under an atmosphere of N_2, was treated dropwise with 2.6 ml CH_3Li (1.4 M solution in ether, 3.64 mmol). To this solution was added a solution of $PhNTf_2$ (800 mg in 10 ml THF, 2.24 mmol). The reaction mixture was stirred at -78 ^{0}C for 10 mins and then was stirred at room temperature for 1 hr. The solvent was removed under vacuum and the residue was chromatographed with EtOAc/hexanes (1:1) to afford 599 mg (90%) **16** as a light yellow film. This material was recrystallized from Et_2O and hexanes to give colorless needles: mp 80-81 ^{0}C; IR ($CHCl_3$) 2958, 1669, 1581, 1489, 1425, 1343, 1142 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 4.69-4.72 and 4.72-4.74 (d, two overlapping sets of doublets, J = 6.0 Hz, 1 H), 3.82-4.02 (m, 2 H), 3.29 (s, 3 H), 2.08-2.81 (m, 7 H), 1.09-1.11 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 191.7 (191.6), 136.4 (136.3), 127.4 (127.3), 125.6 (125.5), 118.6 (q, J = 320.6 Hz), 115.1 (115.1), 74.5 (74.4), 56.5, 46.3 (46.2), 43.5 (43.4), 35.7, 31.0 (31.1), 29.7, 21.0. HRMS (DEI, M$^+$) calcd for $C_{14}H_{16}NO_5F_3S$: 367.0701, found: 367.0684.

Methyl 1-methoxy-6-methyl-1,2,5,6,7,8-hexahydro-8-oxo-3*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (17). To a solution of **16** (550 mg, 1.49 mmol) in 30 ml DMSO, 20 ml MeOH and 2.5 ml Et_3N was added PPh_3 (320 mg, 1.22 mmol) followed by $Pd(OAc)_2$ (37 mg, 0.17 mmol). A stream of CO was bubbled through the solution for 10 mins and the solution was stirred at 68 ^{0}C for 5 hrs under a balloon of CO. The solvent was removed under vacuum, the residue was diluted with chloroform and washed with 0.5 N HCl and brine. The organic layer was dried and the solvent was removed. The residue was chromatographed with $CHCl_3$/EtOAc (1:1) to give 290 mg (70%) **17** as a light yellow solid: mp 123-124 ^{0}C; IR ($CHCl_3$) 2951, 1729, 1700, 1670, 1559, 1516, 1466 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.84-4.85 and 4.86-4.87 (d, two overlapping sets of doublets, J = 5.3 Hz, 1 H), 3.93-4.03 (m, 1 H), 3.74-3.87 (m, 1 H), 3.79 (s, 3 H), 3.27 and 3.28 (two sets of singlets, 3 H), 2.12-2.78 (m, 7 H), 1.08-1.11 (two overlapping sets of doublets, J = 6.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 192.0 (191.8), 164.1, 142.7, 140.1, 121.5, 107.6, 75.00 (74.9), 56.6, 51.2, 47.5 (47.3), 43.3 (43.20), 35.5 (35.5), 31.1 (30.7), 30.1 (30.0), 21.1 (20.9). HRMS (DCI, M + H$^+$) calcd for $C_{15}H_{19}NO_4$: 278.1392, found: 278.1398.

Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.50; H, 6.90; N, 5.05. Found: C, 64.86; H, 6.92; N, 4.97.

5,6,7,8-Tetrahydro-6-methyl-8-oxo-3*H*-pyrrolo[1,2-*a*]indole-9-carboxylate acid (5). To a suspension of **17** (290 mg, 1.05 mmol) and LiBr (500 mg, 5.7 mmol) in 10 ml CH_3CN was added chlorotrimethylsilane (0.61 ml, 4.8 mmol). The reaction mixture was allowed to stir at 55 ^{0}C under an atmosphere of N_2 for 10 hrs. The reaction was quenched by the addition of 2 ml H_2O, the resulting mixture was diluted with chloroform and

washed with brine. The organic phase was dried and concentrated. The residue was chromatographed with CH_2Cl_2/EtOAc (1:1) to give 205 mg (85%) **5** as a white solid: mp 216-218 °C. The melting point, ^1H NMR, and IR spectral data for this sample are identical to those reported by Rebek.[7] ^{13}C NMR ($CDCl_3$) δ 197.8, 163.8, 149.1, 143.8, 134.2, 123.9, 119.1, 103.7, 50.9, 44.6, 31.2, 29.8, 21.0.

***trans*-2-Bromo-2,3,5,6,7,8-hexahydro-1-hydroxy-6-methyl-8-oxo-1-*H*-pyrrolo[1,2-*a*]indole-9-carboxylic acid (22).** A solution of **5** (160 mg, 0.69 mmol) in 10 ml THF and 2 ml H_2O was treated dropwise with 0.12 M Br_2/H_2O solution in 1 ml aliquots at 10-min intervals until TLC showed that no starting material was left. This solution was diluted with chloroform and washed with saturated sodium bisulfite and brine. The organic phase was dried and concentrated. The residue was chromatographed with $CHCl_3$/EtOAc (1:1) to give 181 mg. (80%) of **22** as a light yellow solid: mp 177-180 °C (this material was used in the next reaction without further purification). The melting point, ^1H NMR, and IR spectral data of this sample are identical to those was reported by Rebek.[7] ^{13}C NMR ($CDCl_3$) δ 198.3 (1982), 165.2 (165.1), 145.6 (145.5), 142.1 (142.1), 119.6, 108.8, 75.4 (75.3), 52.8 (52.8), 48.9 (48.8), 44.6 (44.5), 31.5 (31.2), 29.3 (29.3), 20.9.

***trans*-, and *cis*-1-Azido-2,3,5,6,7,8-hexahydro-2-hydroxy-6-methyl-8-oxo-1-*H*-pyrrolo[1,2-a]indole-9-carboxylate acid (20 and 21).** To a solution of **22** (170 mg, 0.52 mmol) in 10 ml DMF was added a solution of NaN_3 (600 mg, 9.23 mmol) in 2 ml H_2O. The mixture was heated at 75 °C for 2 hrs when the solvent was removed under reduced pressure. The residue was diluted with chloroform and washed with brine (the pH of the brine was preadjusted to 4). The solvent was dried and removed in vacuo. The residue was chromatographed with EtOAc/$CHCl_3$ (1:1) to give 110 mg (74%) **20** as a white solid (this material was used in the next reaction without further purification): mp 168-188 °C (slowly decomposed). The ^1H NMR and IR spectral data of **20** are identical to those reported by Rebek.[7] ^{13}C NMR ($CDCl_3$) δ 197.5 (197.4), 163.2, 142.7, 142.1, 119.3, 110.0, 78.4 (78.3), 63.1 (63.1), 52.0 (52.0), 44.5, 31.2 (31.0), 29.4 (29.3), 20.7 (20.6). The *cis*-isomer **21** was further eluted with EtOAc/MeOH (9:1) to give 24 mg (16%) as light yellow film. IR ($CHCl_3$) 3358, 2960, 2107, 1699, 1602, 1477, 1424, 1377 cm^{-1}; ^1H NMR ($CDCl_3$ with a few drops of DMSO, 400 MHz) δ 5.36-5.38 (two overlapping sets of doublets, J = 5.8 Hz, 1 H), 4.83-4.93 (m, 1 H), 4.14-4.21 (two overlapping sets of dd, J = 11.3, 7.1 Hz, 1 H), 3.68-3.75 (two overlapping sets of dd, J = 11.2, 7.7 Hz, 1 H), 3.63 (brs, 1 H), 2.30-2.88 (m, 5 H), 1.18-1.20 (two overlapping sets of doublets, J = 5.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 197.9, 163.6, 143.1 (143.0), 141.0 (141.0), 119.0, 110.4, 73.5 (73.5), 58.9 (58.8), 49.28, 44.8 (44.7), 31.3, 29.6 (29.6), 21.0 (20.9).

Ethyl *trans*-1-azido-2,3,5,6,7,8-hexahydro-2-[(methylsulfonyl)oxy]-6-methyl-8-oxo-1-*H*-pyrrolo[1,2-*a*]indole-9-carboxylate acid (25). A solution of **20** (110 mg, 0.38 mmol) in 10 ml THF and 0.3 ml Et_3N was treated dropwise with 0.3 ml MsCl. This mixture was stirred at room temperature for 15 mins and then was heated at 60 °C for 5 mins and then 1 ml absolute ethanol was added dropwise. The resulting solution was stirred at room temperature for another 15 mins. The reaction mixture was diluted with chloroform and washed with brine. The organic phase was dried and concentrated to give a yellow solid. This material was resubjected to the reaction conditions (10 ml THF, 0.2 ml Et_3N, and 0.2 ml MsCl) to complete consumption of the starting material. After workup the organic phase was dried and concentrated. The residue was

chromatographed with EtOAc to give 136 mg (91%) of **25** as a colorless film which could be recrystallized from EtOAc/hexanes to give a white solid: mp 139-142 ^{0}C; IR ($CHCl_3$) 2959, 2111, 1729, 1672, 1562, 1515, 1475, 1312, 1132 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.36 (d, J = 3.9 Hz, 1 H), 5.28 and 5.30 (two sets of singlets, 1 H), 4.25-4.38 (m, 3 H), 4.15 (two overlapping sets of d, J = 13.2 Hz, 1 H), 3.10 (s, 3 H), 2.20-2.83 (m, 5 H), 1.35 (t, J = 7.2 Hz, 3 H), 1.13 (d, J = 6.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 191.4, 162.2, 141.0 (140.9), 137.4, 122.6, 109.9 (109.8), 83.7 (83.6), 62.4 (62.3), 60.6, 50.3 (50.2), 47.5 (47.4), 38.6, 30.9 (30.8), 30.1, 21.1, 14.2. HRMS (DEI, M$^+$) calcd for $C_{16}H_{20}N_4O_6S$: 396.1103, found: 396.1093.

Anal. Calcd for $C_{16}H_{20}N_4O_6S$: C, 48.48; H, 5.09; N, 14.13. Found: C, 48.55; H, 5.10; N, 14.04.

Ethyl *trans*-1-azido-2,3-dihydro-8-hydroxy-2-[(methylsulfonyl)oxy]-6-methyl-1-*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (26). A solution of azido-mesylate **25** (136 mg, 0.34 mmol) in 20 ml EtOAc was heated at 70 ^{0}C. This solution was treated dropwise with a solution of DDQ (77 mg 0.34 mmol) in 3 ml EtOAc. The reaction solution was stirred at 70 ^{0}C under an atmosphere of N_2 for 30 mins and then was diluted with EtOAc/hexanes (4:1). The organic phase was washed with water, brine, and then dried and concentrated. The residue was chromatographed with EtOAc to give 108 mg (80%) **26** as a colorless film (this material was used in the next reaction without further purification). IR ($CHCl_3$) 2982, 2114, 1661, 1559, 1504, 1343, 1134 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.64 (s, 1 H), 6.58 (brs, 2 H), 5.49 (d, J = 4.3 Hz, 1 H), 5.43 (brs, 1 H), 4.48 (dd, J = 12.6, 4.5 Hz, 1 H), 4.43 (q, J = 7.1 Hz, 2 H), 4.30 (d, J = 12.8 Hz, 1 H), 3.11 (s, 3 H), 2.40 (s, 3 H), 1.45 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.8, 151.2, 140.8, 136.8, 134.6, 116.7, 109.6, 102.0, 101.6, 83.9, 62.9, 61.7, 50.0, 38.4, 21.6, 14.1. HRMS (DCI, M + H$^+$) calcd for $C_{16}H_{18}N_4O_6S$: 395.1025, found: 395.1016.

Ethyl *trans*-1-azido-7-bromo-2,3,5,8-tetrahydro-2-[(methylsulfonyl)oxy]-6-methyl-5,8-dioxo-1-*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (29). To a solution of **26** (108 mg, 0.27 mmol) in 10 ml THF and 2 ml H_2O was added 0.76 ml AcOH followed by 230 mg NaOAc. The reaction mixture was treated dropwise with Br_2 (0.18 ml, 3.5 mmol). The resulting solution was stirred at room temperature for 15 mins and then was diluted with EtOAc/hexanes (7:3). The organic phase was washed with saturated sodium bisulfite, saturated $NaHCO_3$, and brine. The solvent was dried and removed to give a yellow solid. This material was chromatographed with EtOAc/CH_2Cl_2 (1:1) to give 122 mg (91%) **29** as a brilliant yellow solid: mp 155-156 ^{0}C; IR ($CHCl_3$) 2940, 2114, 1731, 1682, 1658, 1589, 1505, 1444, 1331, 1141 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.44-5.46 (m, 1 H), 5.40 (brs, 1 H), 4.62-4.63 (m, 2 H), 4.29-4.47 (two overlapping sets of quartets, J = 7.0 Hz, 2 H), 3.12 (s, 3 H), 2.23 (s, 3 H), 1.41 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.9, 172.2, 161.3, 143.3, 143.1, 141.1, 128.2, 125.2, 111.6, 83.5, 62.3, 61.5, 53.1, 38.7, 16.6, 14.2. HRMS (DEI, M$^+$) calcd for $C_{16}H_{15}N_4O_7SBr$: 485.9845, found: 485.9857.

Ethyl *trans*-1,7-diazido-2,3,5,8-tetrahydro-2-[(methylsulfonyl)oxy]-6-methyl-5,8-dioxo-1-*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (30). A solution of **29** (66 mg, 0.14 mmol) in 10 ml CH_3CN and 2 ml EtOH was treated dropwise with a solution of NaN_3 (500 mg in 6 ml H_2O, 7.69 mmol). The reaction mixture was stirred at room temperature for 1.5 hrs and then poured into brine and extracted with chloroform. The organic phase

was dried and concentrated to give a orange yellow residue. This material was chromatographed with EtOAc/hexanes (7:3) to give 56 mg (92%) **30** as a orange yellow solid (this sample was used in the next reaction without further purification): mp 122-124 ^{0}C (decomposed with evolution of gas); IR ($CHCl_3$) 2942, 2116, 1730, 1682, 1650, 1591, 1503, 1474, 1331, 1111 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.44 (d, J = 4.1 Hz, 1 H), 5.37 (s, 1 H), 4.65 (dd, J = 14.6, 0.7 Hz, 1 H), 4.59 (dd, J = 14.6, 4.2 Hz, 1 H), 4.35-4.44 (m, 2 H), 3.11 (s, 3 H), 1.97 (s, 3 H), 1.41 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 177.2, 175.2, 160.9, 142., 142.2, 129.2, 125.5, 124.3, 111.2, 83.6, 62.4, 61.5, 53.0, 38.7, 14.2, 10.4.

Ethyl *trans*-7-amino-1-azido-2,3,5,8-tetrahydro-2-[(methylsulfonyl)oxy]-6-methyl-5,8-dioxo-1-*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (31). Compound **30** (56 mg, 0.13 mmol) was dissolved in 6 ml of acetone and 8 ml of absolute EtOH. This solution was treated dropwise with 40% aqueous sodium dithionite solution until it became colorless. The mixture was added to brine and extracted with chloroform (2 x 20 ml). The organic phase was dried and then heated in a 90 ^{0}C oil bath under an atmosphere of N_2 for 8 hrs. The solvent was removed in vacuo and then 40 ml toluene was added. The resulting solution was refluxed for 4 hrs as the color of the solution changed from light red to deep red. The solvent was removed and then 10 ml of a solution of Et_2O/EtOAc (1:1) was added. The purple solid material was deposited by filtration to give 31 mg **31**. The mother liquid was chromatographed with EtOAc/CH_2Cl_2 (1:1) to give another 6 mg **31** (total yield 70%): mp 218-221 ^{0}C (decomposition); IR ($CHCl_3$) 3621, 2977, 2114, 1729, 1685, 1608, 1522, 1477, 1335 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.42 (dt, J = 4.2, 1.0, 0.75 Hz, 1 H), 5.36 (d, J = 0.75 Hz, 1 H), 5.14 (brs, 2 H), 4.70 (dd, J = 14.8, 0.75 Hz, 1 H), 4.57 (dd, J = 14.8, 4.3 Hz, 1 H), 4.34-4.44 (two overlapping sets of quartets, J = 7.0 Hz, 2 H), 3.10 (s, 3 H), 1.86 (s, 3 H), 1.41 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (DMSO) δ 175.9, 175.6, 161.0, 148.5, 140.1, 130.9, 121.4, 109.1, 104.2, 84.9, 62.1, 60.4, 52.7, 37.6, 14.0, 8.3. HRMS (DCI, M + H$^+$) calcd for $C_{16}H_{17}N_5O_7S$: 424.0927, found: 424.0940.

Ethyl *trans*-7-amino-1-aziridino-2,3,5,8-tetrahydro-6-methyl-5,8-dioxo-1-*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (4). To a solution of **31** (56 mg, 0.13 mmol) in 10 ml THF and 1 ml of H_2O was added 0.5 ml Et_3N followed by triphenylphosphine (52 mg, 0.20 mmol). The reaction solution was stirred at room temperature under an atmosphere of N_2 for 6 hrs. The solution was diluted with CH_2Cl_2 and then washed with brine. The organic phase was dried and concentrated. The residue was chromatographed with EtOAc/$CHCl_3$/MeOH (5:4:1) to give 32 mg (80%) **4** as a purple solid: mp > 200 ^{0}C (slowly decomposed); IR ($CHCl_3$) 3684, 3621, 2978, 1723, 1678, 1610, 1566, 1507, 1476 cm^{-1}; ^{1}H NMR spectrum of **4** gives broad signals for hydrogens on carbons 1-3 as well as on the aziridine nitrogen. In addition, two sets of signals were observed for C^1 and C^{10} in the ^{13}C NMR spectrum of **4**. These can be explained since **4** exists as a mixture of two invertomers.[15] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.04 (brs, 2 H), 4.29-4.44 (m, 3 H), 4.23 (dd, J = 14.3, 2.7 Hz, 1 H), 3.40-3.90 (m, 2 H), 1.78 (s, 3 H), 1.38 (t, J = 7.1 Hz, 3 H), 1.24 (brs, 1 H); ^{13}C NMR ($CDCl_3$) δ 177.2, 175.8, 162.4 (162.3), 146.9, 146.6, 130.8, 121.2, 108.8, 106.2, 60.6, 50.8, 38.6 (38.4), 32.3, 14.4, 7.8. HRMS (DEI, M$^+$) calcd for $C_{15}H_{15}N_3O_4$: 301.1063, found: 301.1056.

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