# Syntheses of C12,N13 Heterocyclic Bridged Fused Indenopyrrolocarbazoles

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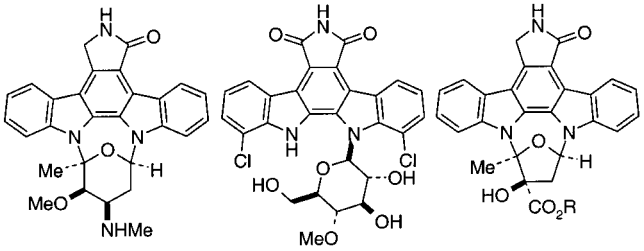
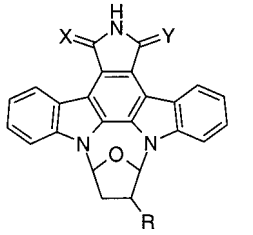
Tandem alkylation/cyclization of indenopyrrolocarbazole **4a**, a C12 carbon analogue of indolocarbazole K252c, was carried out by general solid-phase and solution-phase methods. Alkylation of fused pyrroloindenylcarbazole **4a** derivatives with appropriate monoacetals of diketones afforded the corresponding C12-substituted acetal alcohols. Acid-catalyzed cyclization of these adducts yielded C12,N13-bridged tetrahydrofuran, pyran, and dioxane compounds **10**−**13**.

## Introduction

Over 50 alkaloids of the indolocarbazole family[1] have been characterized including the well-known staurosporin,[2] rebeccamycin,[3] and K252a.[4] Key features of this

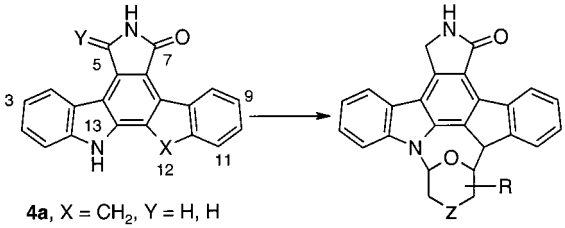



family include an indolocarbazole heterocyclic core with a fused lactam or imide ring and a pendant sugar (pyranose or furanose). The novel structure of these natural products and their diverse biological properties, especially with regard to cell signaling, growth, and proliferation, have stimulated synthetic interest toward the preparation of biologically active analogues of this family of compounds.[5] For example, simple tetrahydrofuran analogues **1**−**3** of arcyriaflavin A (**4b**) and staurosporine aglycon K252c (**4c**) have been reported to be PKC[6] and chk1 kinase[7] inhibitors.



**1**, X = O, Y = O, R = H
**2**, X = $H_2$, Y = O, R = H
**3**, X = $H_2$, Y = O, R = alkyl

As part of our work in preparing ATP competitive kinase inhibitors, we explored solid-phase and solution-phase chemistries to synthesize C12,N13 heterocyclic bridged fused indenopyrrolocarbazoles **5** by a tandem alkylation/cyclization process beginning with 13*H*-indeno-[2,1-*a*]pyrrolo[3,4-*c*]carbazole (**4a**,[8] a C12 analogue of **4c**).



**4a**, X = $CH_2$, Y = H, H
**4b**, X = NH, Y = O (arcyriaflavin A)
**4c**, X = NH, Y = H, H (K252c)

**5**
Z = bond, $CH_2$, O

## Results and Discussion

Solid-phase chemical techniques were well suited for the rapid preparation of analogues of **4a**. Indeed, the solubility and reactivity characteristics of **4a** initially made traditional solution-phase chemistry quite problematic. For example, the acidities of the indole, the lactam, and the C12 hydrogens were comparable, and the behavior of **4a** in the presence of a variety of organic and inorganic basic reagents appeared variable. Presumably, oxidation at C12 and C5 occurred readily in the presence of such bases. To overcome these solubility, selectivity, and reactivity issues, solid-phase chemical techniques were initially investigated.

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(2) For leading references, see: Schupp, P.; Eder, C.; Proksch, P.; Wray, V. V.; Schneider, B.; Herderich, M.; Paul, V. V. *J. Nat. Prod.* **1999**, *62*, 959−62.
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(5) Pindur, U.; Kim, Y.-S., Mehrabani, F. *Curr. Med. Chem.* **1999**, *6*, 26−69 and references therein.
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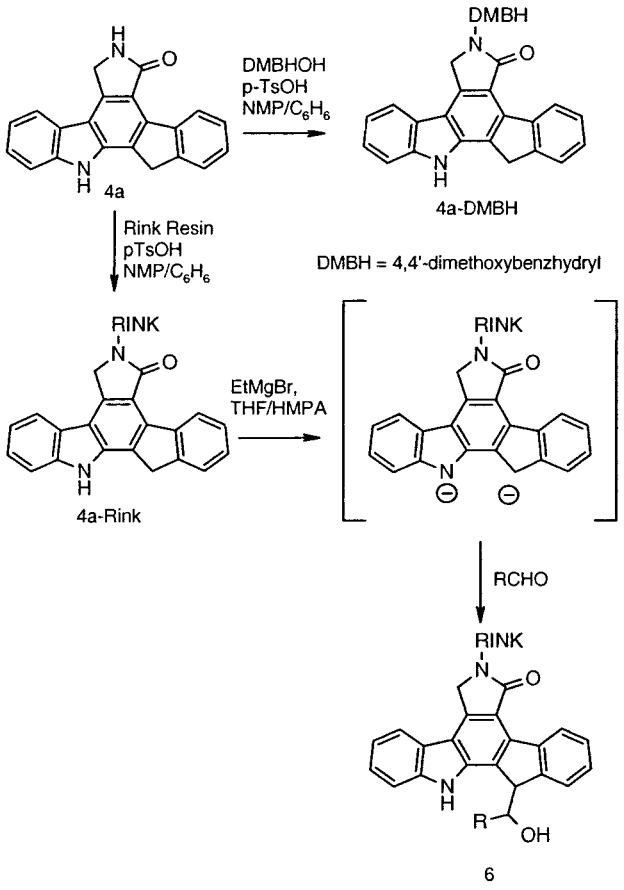
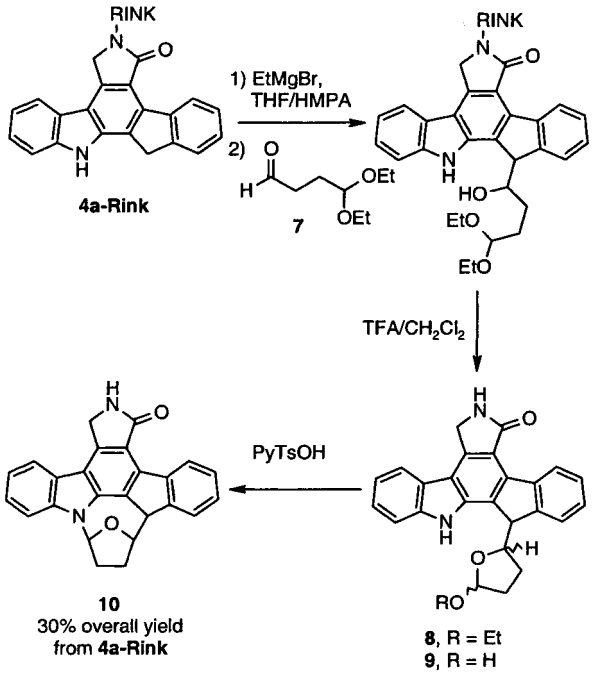
**Scheme 1. Alkylation of 4a-Rink with Aldehydes**




In model reactions with 4,4′-dimethoxybenzhydrol, the lactam of indenopyrrolocarbazole **4a** could be selectively alkylated to give **4a-DMBH** (Scheme 1).[9] As reported eleswhere,[9] the relatively nucleophilic lactam nitrogen provided an appropriate handle to covalently link **4a** onto a resin, and the search for a suitable linker/resin combination resulted in the selection of Rink acid resin (0.64 mmol/g, Calbiochem-Novabiochem Corp). Thus, TsOH-catalyzed dehydrative coupling of **4a** with Rink acid resin proceeded efficiently to give material (**4a-Rink**) whose loading was determined by cleavage with 1% TFA in $CH_2Cl_2$ to be 0.50 mmol/g.[9]

This mode of attachment provided the additional benefit of protecting the lactam from unwanted functionalization. The crystal strucutres of staurosporin bound to PKA[10] and cdk2[11] as well as molecular modeling studies[12] of other indolopyrrolocarbazoles and bisindoylmaleimdes indicated the lactam/imide group of these molecules participates in the same key H-bonding interactions as the natural ligand ATP.[5] Thus, in this series of analogues, an unsubstituted lactam ring was considered an essential element of the pharmacaphore for ATP site recognition.

**Scheme 2. Alkylation of 4a-Rink with 7**




In work described more completely elsewhere,[9] treatment of **4a-Rink** with excess EtMgBr afforded an anionic species that could be alkylated selectively at C12 with aldehydes and ketones (Scheme 1) to ultimately yield a mixture of diastereomeric alcohols **6**. As shown in Scheme 2, it was envisioned that a similar reaction with monoprotected dialdehydes (e.g., **7**) and/or monoprotected ketoaldehydes would also afford the expected secondary alcohols, which could then undergo acid-catalyzed cyclization to afford compounds such as **5**.[13]

In the first example, alkylation of **4a-Rink** with 4,4-diethoxybutyraldehyde (**7**)[14] followed by cleavage with 1% TFA in $CH_2Cl_2$ afforded a mixture of adducts (Scheme 2). Analyses of these products by LC/MS suggested that the mixture consisted of diastereomeric cyclic acetals **8**, hemiacetals **9**, and the fully cyclized adduct **10**. Although reversed-phase preparative HPLC could be used to isolate individual reaction products, pyridinium tosylate-catalyzed equilibration of the complex product mixture afforded predominantly a single diastereomeric product (**10**) in 30% overall yield after isolation by preparative HPLC.

The methodology depicted in Scheme 2 was used to prepare the C12,N13 heterocyclic bridged compounds **11**−**13** shown in Scheme 3. The ketones **14**[15] and **15**[16] were prepared by literature methods. Ketone **16** was prepared by alkylating diethoxyethanol[17] with methallyl chloride followed by ozonolysis of the resulting allyl ether.

The THF-bridged compound **11** was isolated as a single isomer, presumably with the same relative stereochemistry as obtained for the preparation of **10**; in contrast, the pyran (**12**) and dioxane (**13**) bridged derivatives were

(9) Singh, J.; Hudkins, R. L.; Mallamo, J. P.; Underiner, T. L.; Tripathy, R. US patent 6,127,401, 2000. Tripathy, R.: Learn, K. S.; Reddy, D.; Iqbal, M.; Singh, J.; Mallamo, J. M. *Tetrahedron Lett.* **2002**, *43*, 217−20.

(10) Prade, L.; Engh, R. A.; Girod, A.; Kinzel, V.; Huber, R.; Bossemeyer, D. *Structure* **1997**, *5*, 1627−37.

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(12) Furet, P.; Caravatti, G.; Lydon, N.; Priestle, J. P.; Sowadski, J. M.; Trinks, U.; Traxler, P. *J. Comput.-Aided Mol. Des.* **1995**, *9*, 465−72. Toledo, L. M.; Lydon, N. B.; Elbaum, D. *Curr. Med. Chem.* **1999**, *6*, 775−805.

(13) A similar strategy was implemented in the total syntheses of indolocarbazole K252a: Wood, J. L.; Stoltz, B. M.; Dietrich, H.-J. *J. Am. Chem. Soc.* **1995**, *117*, 10413−14.

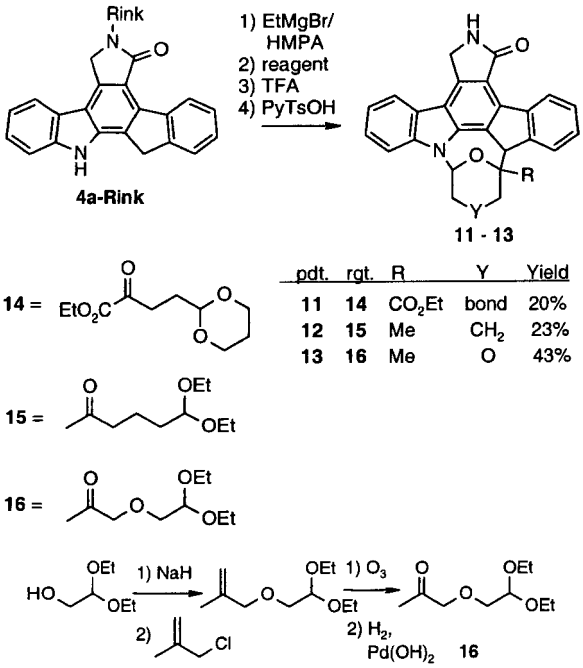
(14) Paquette, L. A.; Backhaus, D.; Braun, R.; Underiner, T. L.; Fuchs, K. *J. Am. Chem. Soc.* **1997**, *119*, 9662−71.

(15) Schmidt, U.; Riedl, B. *Synthesis* **1993**, 809−14.

(16) Brenner, J. E. *J. Org. Chem.* **1961**, *26*, 22−7.

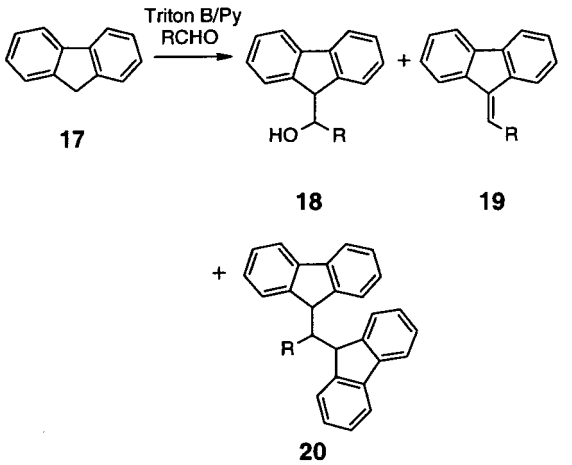
(17) Bernard, D.; Doutheau, A.; Gore, J. *Synth. Commun.* **1987**, *17*, 1807−14.

**Scheme 3. Tandem Alkylation/Cyclization 4a-Rink with Ketones 14−16**




prepared as a mixture of diastereomers that were separated by preparative reversed-phase HPLC. Attempts to assign relative stereochemistry to the adducts **10**−**13** by crystallographic techniques are curently in progress. The stereochemical assignment of **10** will be addressed in the following section.

Preparing multigram quantities of the bridged indenopyrrolocarbazoles **5** via the solid-phase method described above proved impractical and uneconomical with respect to the resin, reagents, and solvents. As alluded to earlier, attempts to alkylate **4a** under strongly basic conditions proved problematic, and typically only highly insoluble material was recovered from these reactions. It had been reported that Triton B-catalyzed alkylation of flourene (**17**) with aldehydes and ketones gave product mixtures consisting of addition (**18**), addition−elimination (**19**), and other products (e.g., **20**).[18] The product distribution depended on the particular reaction conditions and the aldehydes utilized.




This method proved unsuccessful when applied to the reaction of **4a** with 1,3-dioxane-protected succinaldehyde **21**.[19] On the other hand, reaction of **4a-TBDPS** with aldehyde **21** in the presence of Triton B proceeded smoothly to afford a 9:1 mixture of isomers **22-tBDPS** and **23-tBDPS** as determined by HPLC analysis of the crude reaction mixture. Analysis by TLC (silica gel) indicated that the $\Delta R_f$ for **22-tBDPS** and **23-tBDPS** was >5, and so these isomeric alcohols were easily separated by column chromatography (Scheme 4). To confirm that the 9:1 product ratio was a thermodynamic product distribution, the individual alcohols were treated with Triton B, and each returned an exclusive 9:1 mixture of **22-tBDPS** and **23-tBDPS** as determined by HPLC. Whether this equilibration occurred by simple deprotonation of the indenyl methine (C12) followed by preferential diastereofacial protonation or by regeneration of the aldehyde followed by alkylation is not certain at this time. However, the latter seems less likely since alkylation of **4a-tBDPS** with only 1 equiv of aldehyde **21** inevitably led to incomplete conversion to **22-tBDPS** and **23-tBDPS** due to the apparent instability of the aldehyde to the basic reaction conditions. If the latter equilibration mechanism were operational, an equilibrated mixture of alcohols *and* **4a-tBDPS** would be expected; however, only **22-tBDPS** and **23-tBDPS** were detected by HPLC.

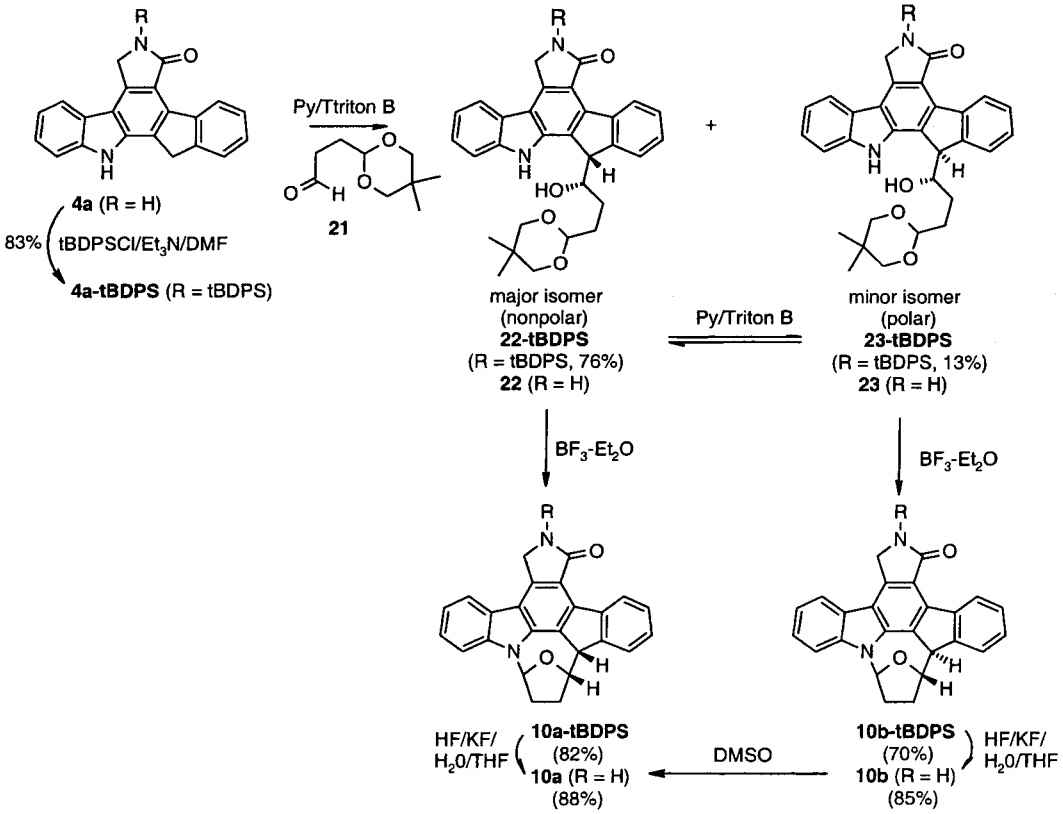
These observations (i.e., thermodynamic stability and apparent $\Delta R_f$) have implications for assigning the relative stereochemistry of the isomeric alcohols **22-tBDPS** and **23-tBDPS** and, ultimately, compound **10**. Newman projections (viewed down the carbinol (C1′)−indene (C12) carbon bonds) for conformations of **22-tBDPS** and **23-tBDPS** that would facilitate an intramolecular hydrogen bond between the indole NH and the oxygen of the hydroxyl group are depicted in Figure 1. The stabilization afforded by such an intramolecular interaction is balanced by the restricted rotation around the C1′−C2′−C3′−C4′ bonds of the pendant alkyl chain imposed by the aromatic core and/or the indene hydrogen. If the balance favors formation of an intramolecular H-bond, the overall basicity of the molecule would be expected to be relatively low (i.e., the relative $R_{f,\text{silica}}$ would be high). On the other hand, if the energetic cost of achieving a conformation that would facilitate the formation of an intramolecular H-bond is too high, the overall basicity of this alcohol would be expected to be relatively high (i.e., the relative $R_{f,\text{silica}}$ would be low). The degrees of freedom along the C1′−C4′ bonds in the conformation of **23-tBDPS** depicted in Figure 1 are more severely restricted than those for **22-tBDPS**. That is to say, for **23-tBDPS**, conformational restrictions inhibit the formation of an intramolecular H-bond, and this may account for the alcohol's low $R_f$ ($R_{f,\text{silica}} = 0.1$). For **22-tBDPS**, a conformation conducive for intramolecular H-bonding can more readily be accommodated, and this may account for its observed high $R_f$ ($R_{f,\text{silica}} = 0.5$). These arguments (and those that follow) suggest that **22-tBDPS** ($R_{f,\text{silica}} = 0.5$) is the preferred product from alkylating **4a-tBDPS** with aldehyde **21**.

Treatment of each isomeric alcohol **22-tBDPS** and **23-tBDPS** with $BF_3$ etherate afforded diastereomers **10a-tBDPS** and **10b-tBDPS**, respectively. Under these reaction conditions, various degrees of desilylation of the lactam occurred. If the unprotected material was desired, it was more efficient to treat this crude product mixture

(18) Ghera, E.; Sprinzak, Y. *J. Am. Chem. Soc.* **1960**, *82*, 4945−52.

(19) Khanna, I. K.; Weier, R. M.; Yu, Y.; Collins, P. W.; Miyashiro, J. M.; Koboldt, C. M.; Veenhuizen, A. W.; Currie, J. L.; Seibert, K.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1619−33.

**Scheme 4. Solution-Phase Tandem Alkylation/Cyclization of 4a-tBDPS with Aldehyde 21**



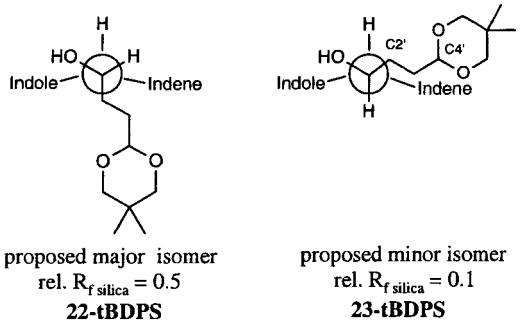




**Figure 1.** Newman projections of alcohols **22-tBDPS** and **23-tBDPS** depicting the orientation for intramolecular H-bonding.

with aqueous HF buffered with KF to afford **10**.[20] Otherwise, chromatography was necessary to separate **10-tBDPS** from **10**.

It was observed by $^1$HNMR and HPLC that diastereomer **10b** completely isomerized to **10a** in DMSO (Scheme 4). Presumably, epimerization of the C12 methine of **10b** occurred to yield the apparently more stable diastereomer **10a**. To rationalize these observations, compuational chemistry studies were carried out. Depictions of the SYBYL[21]-minimized structures (with AM1 geometry optimization) for each isomer of **10** are shown in Figure 2. A structure in which the N13 and C12 atoms are bridged by a *trans*-substituted THF ring is undoubtedly too strained to be isolated or observed. The most prominent structural feature that distinguishes the two isomers depicted in Figure 2 is the orientation of the plane defined by the THF ring relative to the planar aromatic portion of the molecule. For **10a**, the angle between these planes is slightly less than 90°; in the case of **10b**, this angle is nearly 220° (Figure 2). As a consequence, the *endo*-hydrogens (shown as dark gray in the second right-

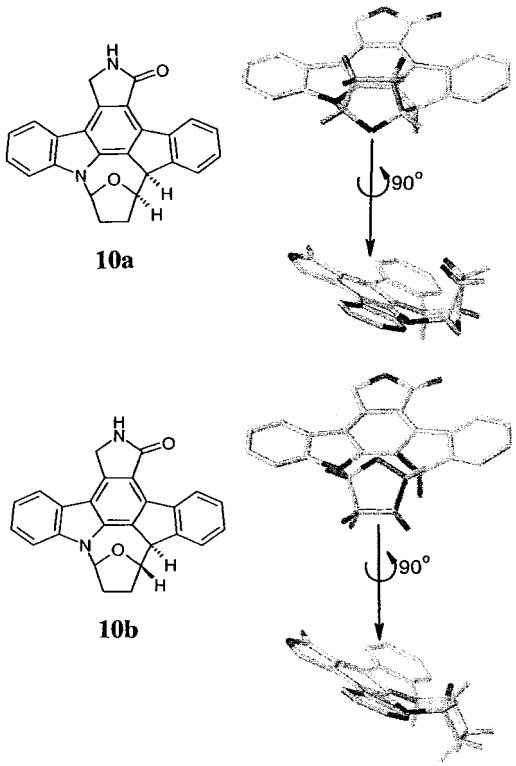



**Figure 2.** SYBYL[21]-minimized structures of **10a** and **10b**.

(20) Kendall, P. M.; Johnson, J. V.; Cook, C. E. *J. Org. Chem.* **1979**, *44*, 1421−24.

(21) SYBYL Molecular Modeling System (version 6.6), Tripos Associates, St. Louis, MO. Please see the Experimental Section for details concerning generation of these minimized structures.

hand structure of Figure 2) on the THF ring of **10a** appear to reside in the aromatic ring current. Thus, the signals in the $^1$HNMR sprectrum for the *endo*-protons would be expected to appear significantly upfield of those of the *exo*-protons.[6,22,] Since the *exo*- and *endo*-hydrogens for **10b** are situated in more similar environments, a less dramatic difference in chemical shifts for these protons in the H NMR spectrum would be expected. Signals in $^1$H NMR ($CDCl_3$) for these methylene protons of **10a-tBDPS** appeared at $\delta$ 0.93, 1.14, 2.05, and 2.27, while those for **10b-tBDPS** appeared at $\delta$ 2.60, 2.69, 2.91, 3.05. Also evident in Figure 2 is the closer proximity of the indene C12 methine to the pair of *endo* THF methylene protons for isomer **10b** compared to that for the major isomer **10a**. To confirm the relative proximity of these protons, NOE experiments were carried out, and the minor isomer **10b-tBDPS** revealed signal enhancements between the indene C12 methine and *endo* THF methylene protons; such an effect was not observed for the major isomer **10a**. These spectral data support the assignment of the major stereoisomer to structure **10a** and are consistent with the proposed structure assigned to its alcoholic precursor **22-tBDPS**.

These computational chemistry calculations also offer an explanation for the observed isomerization of **10b** to **10a**. As shown in Figure 2, two eclipsing interactions are apparent for **10b**: the C12 methine hydrogen with the carbon−carbon bond of the bridging THF ring and the indene carbon−carbon bond with the carbon−oxygen bond of the THF ring (shown as dark gray bonds in the third right-hand structure of Figure 2). On the other hand, **10a** enjoys a more stable *gauche* conformation for these same groups. Computational chemistry (AM1) calculations[21] indicate that **10a** is thermodynamically more stable than **10b** by 2.14 kcal/mol. Thus, the observed epimerization of **10b** to **10a** is consistent with theoretical calculations and supports the stereochemical assignment that was made on the basis of the spectral evidence.

Finally, chiral HPLC (Chiralcel OD) was utilized for the preparative separation of the constitutive enantiomers of **10a-tBDPS**. This method provided baseline resolution of the two enantiomers. The individual isomers were deprotected as described before to afford each enantiomer of **10a**. The optical purity of each enantiomer so isolated was assessed by analytical chiral HPLC and was found to be 97% ee and 90% ee, respectively. Preparative chiral HPLC separation of the enantiomers of **10a** was impractical for solubility reasons.

## Conclusion

General solid-phase and solution-phase routes to prepare heterocyclic bridged derivatives of fused indenopyrrolocarbazoles were developed and involved a tandem alkylation/cyclization reaction sequence. This represents a method for the concise preparation of C12,N13-bridged indenopyrrolocarbazole analogues **5** starting from the C12 carbon analogue **4a** of the natural product **4c**. The structures of **10a** and **10b** were assigned on the basis of their NMR spectral data, the chromatographic characteristics of their precursor alcohols **22-tBDPS** and **23-tBDPS**, and the predicted thermodynamic stability of **10a** over **10b**. The biological activity of these new compounds is currently under investigation and will be reported in due course.

## Experimental Section

**General Methods.** All reagents and solvents were obtained from commercial sources and used without further purification. HMPA was dried over CaH and decanted prior to use. NMR spectra were recorded at either 300 or 400 MHz (proton) and 100 MHz (carbon) in the solvent indicated with TMS as an internal reference. Coupling constants ($J$) are given in hertz. Flash chromatography was carried out in the solvents indicated with Biotage Flash silica gel cartridges. Preparative HPLC was carried out with a Zorbax RX-8, 4 × 25 cm column eluted with a mixture of MeCN and water containing 0.1% trifluoroacetic acid. Elemental analyses were carried out by Micro-Analysis, Inc. (Wilmington, DE). Low-resolution mass spectra were obtained by ion spray ionization. High-resolution mass spectrometry (FAB) were carried out by M-Scan (West Chester, PA).

**Preparation of Rink-Resin-Bound 4a (4a-Rink).** A three-neck round-bottom flask fitted with an overhead mechanical stirrer and a Dean−Stark trap was sequentially charged with Rink acid resin (10.00 g, 0.64 mmol/g), 1-methyl-2-pyrolidinone (80 mL), benzene (350 mL), **4a**[8] (3.00 g), and *p*-toluenesulfonic acid (1.00 g). The reaction mixture was warmed to reflux for 20 h, and then filtered. The resin was washed with THF (5 × 175 mL) and the filtrate set aside. The resin was then sequentially washed with DMSO (4 × 100 mL), 2% aqueous $NaHCO_3$ (4 × 100 mL), water (4 × 100 mL), DMSO (2 × 200 mL), THF (4 × 100 mL), and ethyl acetate (4 × 100 mL). The resin was dried under vacuum (24 h) to afford 11.70 g (0.47 mmol/g) of **4a-Rink**.

The original THF washings were evaporated, the residue was diluted with water (750 mL), and the resulting precipitate was filtered and sequentially washed with water, 2% aqueous $NaHCO_3$ (4 × 100 mL), and water (4 × 100 mL). After the precipitate was dried under vacuum, **4a** (1.28 g) was recovered.

**General Procedure for the Solid-Phase Synthesis of Bridged Indenopyrrolocarbazoles (10a).** To a suspension of **4a-Rink** (1.25 g) in THF (24 mL) was added a 1.0 M solution of EtMgBr in THF (6.25 mL), and the reaction was stirred for 1 h prior to the addition of HMPA (5.0 mL). After the reaction was stirred for 10 min, diethoxybutyraldehyde[14] (3.0 g) was added, and the reaction was stirred for 20 h. The reaction was quenched with 10% aqueous $NH_4Cl$ (5 mL) and filtered. The resin was successively washed with 10% aqueous $NH_4Cl$ (3 × 10 mL), water (3 × 10 mL), THF (3 × 10 mL), DMF (3 × 10 mL), water (3 × 10 mL), THF (3 × 10 mL), and ether (3 × 10 mL). The resin was dried under vacuum, taken up in methylene chloride (15 mL), and treated with trifluoroacetic acid (0.15 mL). After being stirred for 1 h, the reaction was filtered, and the filtrate was evaporated. The resulting residue was taken up in methylene chloride (20 mL) and treated with pyridinium tosylate (50 mg). After being stirred for 4 h, the reaction mixture was washed with saturated aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. After filtration and solvent evaporation, the residue was purified by preparative HPLC (60% MeCN/water). The appropriate fractions were neutralized by addition of solid $NaHCO_3$ and extracted into methylene chloride (3 × 50 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated to afford 70.2 mg (39%) of **10a** as a white powder which had the following characteristics: $^{13}$C NMR (DMSO-$d_6$) $\delta$ 171.7, 143.1, 142.2, 141.3, 140.0, 139.9, 136.5, 129.1, 127.8, 127.3, 127.0, 126.7, 124.0 (2C), 122.5, 121.5, 121.4, 118.2, 112.0, 88.0, 79.1, 56.5, 45.5, 33.3, 24.7; $^1$H NMR (DMSO-$d_6$) $\delta$ 9.26 (d, $J$ = 7.5, 1H), 8.63 (s, 1H), 8.05 (d, $J$ = 7.7, 1H), 7.90 (d, $J$ = 8.3, 1H), 7.75 (d, $J$ = 7.0, 1H), 7.53 (dd, $J$ = 8.2, 7.2, 1H), 7.45 (dd, $J$ = 7.5, 7.4, 1H), 7.38 (dd, $J$ = 8.6, 7.4, 1H), 7.34 (dd, $J$ = 7.7, 7.2, 1H), 6.88 (d, $J$ = 6.2, 1H), 5.64 (app dt, $J$ = 8.6, 3.7, 1H), 4.95 (s, 2H), 4.57 (d, $J$ = 3.7, 1H), 2.23 (m, 1H), 1.97 (m, 1H), 0.96 (m, 1H), 0.63 (m, 1H),

(22) Emsley, J. W.; Feeney, J.; Sutcliffe, L. H. *High Resolution Nuclear Magnetic Resonance Spectroscopy*; Pergamon: New York, 1975; Vol. 1.

also $CH_2Cl_2$ peak at 5.75 (s, 0.2 H); MS (*m*/*z*) for M + H ($C_{25}H_{19}N_2O_2$), calcd 379, obsd 379. Anal. Calcd for $C_{25}H_{18}N_2O_2$ with 0.1($CH_2Cl_2$): C, 77.92; H, 4.74; N, 7.24. Found: C, 77.91; H, 4.74; N, 7.22.

**Preparation of 11.** Following the general procedure, **4a-Rink** (150.2 mg) was alkylated with ethyl 5,5-diethoxy-2-oxopentanoate[15] (**14**, 1.5 mL). After workup and cleavage from the resin, the crude reaction product mixture was taken up in methylene chloride (20 mL) and treated with $BF_3$ etherate (20 uL). After being stirred for 2.5 h, the solution was washed with saturated aqueous $NaHCO_3$ and brine prior to being dried over $MgSO_4$. After filtration and solvent removal, the resulting residue was purified by preparative HPLC (55% → 75% MeCN/water gradient) to afford **11** (6.4 mg, 20%), which had the following properties: $^1$H NMR (DMSO-$d_6$) $\delta$ 9.36 (d, $J$ = 7.7, 1H), 8.68 (s, 1H), 8.00 (d, $J$ = 7.7, 1H), 7.83 (d, $J$ = 8.3, 1H), 7.58−7.15 (m, 5H), 6.97 (d, $J$ = 5.9, 1H), 4.93 (s, 2H), 4.82 (s, 1H), 4.48 (q, $J$ = 7.1, 2H), 2.42−2.10 (m, 2H), 1.37 (t, 3H, $J$ = 7.1), 1.25−0.63 (m, 2H); HRMS (*m*/*z*) for M + H$^+$ ($C_{28}H_{23}N_2O_4$), calcd 451.1642, obsd 451.1658.

**Preparation of 12.** Following the general procedure, **4a-Rink** (74.3 mg) was alkylated with 1,1-diethoxy-5-hexanone[16] (**15**; 0.75 mL), cyclized, and purified by preparative HPLC (65% MeCN/water) to afford **12a** (2.10 mg, 15%) and **12b** (1.06 mg, 8%), which had the following salient spectral properties: (**12a**) $^1$H NMR (DMSO-$d_6$) $\delta$ 9.30 (d, $J$ = 8.3, 1H), 8.55 (s, 1H), 7.97 (d, $J$ = 7.2, 1H), 7.65 (d, $J$ = 8.5, 1H), 7.59 (d, $J$ = 7.5, 1H), 7.48 (m, 1H) 7.39−7.15 (m, 3H), 6.31 (m, 1H), 5.02 (s, 1H), 4.88 (s, 2H), 0.88 (s, 3H); HRMS (*m*/*z*) for M + H$^+$ ($C_{27}H_{23}N_2O_2$), calcd 407.1759, obsd 407.1740. (**12b**) $^1$H NMR (DMSO-$d_6$) $\delta$ 9.43 (d, $J$ = 8.1, 1H), 8.59 (s, 1H), 7.99 (d, $J$ = 7.3, 1H), 7.75−7.65 (m, 2H), 7.49 (m, 1H), 7.43 (m, 1H), 7.36−7.25 (m, 2H), 6.75 (s, 1H), 4.91 (s, 2H), 4.50 (s, 1H), 1.95 (s, 3H); HRMS (*m*/*z*) for M + H$^+$ ($C_{27}H_{23}N_2O_2$), calcd 407.1759, obsd 407.1769.

**Preparation of (1,1-Diethoxyethoxy)acetone (16).** To a cold (0 °C) suspension of NaH (2.68 g, 60% dispersion in mineral oil) in THF (150 mL) was added a solution of 1,1-diethoxyethanol[17] (9.00 g) in THF (20 mL). The reaction mixture was stirred at room temperature for 1 h before methallyl chloride (8.0 mL) was added. The reaction mixture was heated to reflux overnight, cooled, and filtered through a plug of Celite. Solvent was removed by rotary evaporation, and the residue was purified by flash chromatography (20% ether/hexane) to give 1,1-diethoxyethyl 2-methyl-1-propenyl ether (11.5 g, 90%), which had the following properties: $^1$H NMR ($CDCl_3$) $\delta$ 4.95 (s, 1H), 4.89 (s, 1H), 4.63 (t, $J$ = 7.3, 1H), 3.67 (s, 2H), 3.80−3.65 (m, 2H), 3.65−3.50 (m, 2H), 3.45 (d, $J$ = 5.2, 1H), 1.73 (s, 3H), 1.19 (t, $J$ = 7.2, 6H). Ozonolysis of a chilled (−30 °C) solution of this ether (6.00 g) in EtOAc (80 mL) was carried out until no starting material was detectable by TLC (1 h). At this time, the reaction was purged with oxygen, treated with $Pd(OH)_2$ (150 mg), and stirred under an atmosphere of hydrogen overnight. The catalyst was filtered away, and the filtrate was concentrated by rotary evaporation. The resulting residue was purified by flash chromatography (20% EtOAc/hexane) to afford **16** (4.53 g, 82%), which had the following properties: $^1$H NMR ($CDCl_3$) $\delta$ 4.6 (t, $J$ = 7.2, 1H), 4.13 (s, 2H), 3.80−3.65 (m, 2H), 3.63−3.50 (m, 4H), 2.04 (s, 3H), 1.19, (t, $J$ = 7.0, 6H). Anal. Calcd for $C_9H_{18}O_4$: C, 56.82; H, 9.52. Found: C, 57.13; H, 9.39.

**Preparation of 13.** Following the general procedure, **4a-Rink** (230.2 mg) was alkylated with **16** (1.2 mL). After workup and cleavage from the resin, a portion of the crude reaction product mixture (10.5 mg from 23.7 mg, 44%) was taken up in methylene chloride (20 mL) and treated with $BF_3$ etherate (20 uL). After being stirred for 2.5 h, the solution was washed with saturated aqueous $NaHCO_3$ and brine prior to being dried over $MgSO_4$. After filtration and solvent removal, the resulting residue was purified by preparative HPLC (65% MeCN/water) to afford **13a** (2.34 mg, 27%) and **13b** (1.34 mg, 16%). Adduct **13a** had the following properties: $^1$H NMR ($CDCl_3$) $\delta$ 9.35−9.20 (m, 1H), 7.87 (d, $J$ = 7.6, 1H), 7.62 (d, $J$ = 7.0, 1H), 7.60−7.30 (m, 6H), 6.22 (s, 1H), 5.20−4.85 (m, 2H), 4.47 (s, 1H), 3.67 (d, $J$ = 12.7, 1H) 3.52 (d, $J$ = 11.8, 1H), 3.40 (d, $J$ = 12.7, 1H), 3.38 (d, $J$ = 11.8, 1H), 1.91 (s, 3H); HRMS (*m*/*z*) for M$^+$ ($C_{26}H_{21}N_2O_3$), calcd 409.1552, obsd 409.1556. Adduct **13b** had the following properties: $^1$H NMR ($CDCl_3$) $\delta$ 9.58−9.22 (m, 1H), 7.82 (d, $J$ = 7.4, 1H), 7.60−7.40 (m, 3H), 7.37−7.27 (m, 3H), 7.21 (d, $J$ = 8.1, 1H), 5.81 (s, 1H), 5.21 (s, 1H), 5.10−4.80 (m, 2H), 4.59 (d, $J$ = 13.5, 1H), 4.38 (dd, $J$ = 13.5, 5.3, 1H), 4.21 (d, $J$ = 13.1, 1H), 3.82 (d, $J$ = 13.2, 1H), 1.13 (s, 3H); HRMS (*m*/*z*) for M + H$^+$ ($C_{26}H_{21}N_2O_3$), calcd 409.1552, obsd 409.1550.

**Preparation of 6-*tert*-Butyldiphenylsilyl-6,7,12,13-tetrahydro-5*H*-indeno[2,1-*a*]pyrrolo[3,4-*c*]carbazol-5-one (4a-tBDPS).** To a solution of **4a**[8] (6.2 g) in DMF (150 mL) were added TEA (9.7 mL), *tert*-butylchlorodiphenylsilane ((tBDPS)-Cl, 10.5 mL), and a catalytic amount of dimethylaminopyridine. The mixture was heated at 50 °C for 15 h. Additional triethylamine (5.0 mL) and (tBDPS)Cl (5.0 mL) was then added, and the reaction was kept at 50 °C for another 20 h. The reaction was quenched with aqueous $NaHCO_3$ and extracted into EtOAc. The organic layer was washed with water (2 × 100 mL) and brine before being dried over $MgSO_4$. After filtration and solvent evaporation, the resulting residue was triturated with 1:1 ether/hexane to afford the product (9.1 g, 83%). An analytical sample was isolated by flash chromatography (20% EtOAc/hexane) and had the following spectral properties: $^1$H NMR (DMSO-$d_6$) $\delta$ 11.95 (s, 1H), 9.21 (d, $J$ = 1.8, 1H), 7.80−7.20 (m, 16H), 7.13 (dd, $J$ = 8.1, 2.7, 1H), 4.83 (s, 2H), 4.13 (s, 2H), 1.25 (s, 9H). Anal. Calcd for $C_{37}H_{32}N_2OSi$: C, 80.98; H, 5.88; N, 5.11. Found: C, 81.11; H, 5.75.

**Preparation of Racemic (13*R*,1*R*)- and (13*R*,1*S*)-*rel*-13-[3-(5,5-Dimethyl-1,3-dioxan-2-yl)-1-hydroxypropyl]-6,7,-12,13-tetrahydro-5*H*-indeno[2,1-*a*]pyrrolo[3,4-*c*]carbazol-5-one (22 and 23).** A solution of **4a-tBDPS** (1.00 g) in pyridine (20.0 mL) was flushed with argon and treated with 2.5 mL of Triton B (0.45 M in pyridine)[17] and **21**[19] (5 mL). After being stirred for 2 h, the reaction was extracted into EtOAc and washed with 10% aqueous $CuSO_4$ (3 × 50 mL) and brine, and the organic layer was dried over $MgSO_4$. After filtration and solvent evaporation, the residue was purified by flash chromatography (20% → 60% EtOAc/hexane) to first give **22-tBDPS** (990 mg, 76%) and then **23-tBDPS** (167 mg, 13%). These alcohols were analyzed by MS: *m*/*z* for M + H$^+$ ($C_{46}H_{49}N_2O_4Si$), calcd 721, obsd 721. Further characterization was carried out after removal of the tBDPS group by the following method.[20] A solution of **22-tBDPS** (75 mg) in THF (16 mL) was added to an aqueous solution (5.8 mL) of HF (0.175 mL of a 0.1 M aqueous solution) buffered with KF (35.1 mg). The solution was stirred for 24 h, taken up in $CH_2Cl_2$, and washed with aqueous $NaHCO_3$. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 100 mL), and the combined organic layers were immediately passed through a plug of $MgSO_4$. Evaporation of the filtrate left a residue that was triturated with ether (3 × 1 mL) to afford **22** (45 mg, 90%): $^1$H NMR (DMSO-$d_6$) $\delta$ 10.97 (s, 1H) 9.40 (d, $J$ = 7.3, 1H), 8.53 (s, 1H), 8.01 (d, $J$ = 7.7, 1H), 7.78 (d, $J$ = 8.1, 1H), 7.63 (d, $J$ = 7.1, 1H), 7.48 (t, $J$ = 7.4, 1H), 7.42 (t, $J$ = 7.4, 1H), 7.35 (t, $J$ = 7.2, 1H), 7.29 (t, $J$ = 7.2, 1H), 6.35 (d, $J$ = 4.1, 1H), 4.95 (s, 2H), 4.63 (m, 1H), 4.50 (d, $J$ = 3.2, 1H), 4.08 (t, $J$ = 5.1, 1H), 3.30−3.25 (m, 2H), 3.15 (m, 2H), 1.62 (m, 1H), 1.31 (m, 1H), 0.90 (s, 3H), 0.88−0.70 (m, 2H), 0.53 (s, 3H). Anal. Calcd for $C_{30}H_{30}N_2O_4$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.88; H, 6.31; N, 5.66. In a similar manner, **23-tBDPS** was converted to **23**, which had the following properties: $^1$H NMR (DMSO-$d_6$) $\delta$ 11.71 (s, 1H) 9.40 (d, $J$ = 7.6, 1H), 8.52 (s, 1H), 7.99 (d, $J$ = 7.9, 1H), 7.89 (d, $J$ = 7.3, 1H), 7.66 (d, $J$ = 8.1, 1H), 7.48 (t, $J$ = 7.2, 1H), 7.40 (t, $J$ = 7.2, 1H), 7.31 (t, $J$ = 7.5, 1H), 7.28 (t, $J$ = 7.5, 1H), 5.24 (d, $J$ = 3.8, 1H), 4.93 (s, 2H), 4.83 (m, 1H), 4.59 (d, $J$ = 4.5, 1H), 3.98 (t, $J$ = 5.1, 1H), 3.23 (dd, $J$ = 10.9, 2.6, 1H), 3.12 (dd, $J$ = 10.9, 2.6, 1H), 3.03 (d, $J$ = 10.9, 1H), 2.93 (d, $J$ = 10.9), 1.49 (m, 1H), 1.17 (m, 1H), 0.80 (s, 3H), 0.76 (m, 1H), 0.50 (m, 1H) 0.44 (s, 3H). Anal. Calcd for $C_{30}H_{30}N_2O_4$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.99; H, 6.29, N, 5.44.

**Preparation of Racemic (9*R*,12*S*,12a*S*)-*rel*-3,9,10,11,-12,12a-Hexahydro-2-*tert*-butyldiphenylsilyl-9,12-epoxy-indeno[1,2,3-*fg*]indolo[3,2,1-*kl*]pyrrolo[3,4-*i*][1]benzazocin-1-one (10a-tBDPS).** A solution of **22-tBDPS** (185 mg) in

$CH_2Cl_2$ (20 mL) was treated with $BF_3$ etherate (10 uL). After being stirred for 0.25 h, the solution was washed with saturated aqueous $NaHCO_3$ and brine prior to being dried over $MgSO_4$. Removal of solvent by rotary evaporation gave a residue that was purified by flash chromatography (25% EtOAc/hexane) to afford **10a-tBDPS** (129 mg, 82%), which had the following properties: $^1$H NMR (DMSO-$d_6$) $\delta$ 9.08 (d, $J$ = 7.2, 1H), 7.86 (d, $J$ = 8.2, 1H), 7.73 (d, $J$ = 6.9, 1H), 7.70−7.24 (m, 15H), 6.88 (d, $J$ = 5.9, 1H), 5.72 (m, 1H), 4.86 (s, 2H), 4.55 (d, $J$ = 3.3, 1H), 2.30−2.20 (m, 1H), 2.10−1.90 (m, 1H), 1.29 (s, 9H), 1.10−0.90 (m, 1H), 0.73−0.66 (m, 1H); MS (*m*/*z*) for M + Na ($C_{41}H_{36}N_2O_2SiNa$), calcd 639, obsd 639. Anal. Calcd for $C_{41}H_{36}N_2O_2Si$: C, 79.84; H, 5.88; N, 4.54. Found: C, 80.06; H, 5.79, N, 4.40.

**Preparation of Racemic (9*S*,12*R*,12a*S*)-*rel*-3,9,10,11,-12,12a-Hexahydro-2-*tert*-butyldiphenylsilyl-9,12-epoxyindeno[1,2,3-*fg*]indolo[3,2,1-*kl*]pyrrolo[3,4-*i*][1]benzazocin-1-one (10b-tBDPS).** A solution of **23-tBDPS** (25 mg) in $CH_2Cl_2$ (10 mL) was treated with $BF_3$ etherate (3 uL). After being stirred for 0.5 h, the solution was washed with saturated aqueous $NaHCO_3$ and brine prior to being dried over $MgSO_4$. Removal of solvent by rotary evaporation gave a residue that was purified by flash chromatography (silica gel, 25% EtOAc/hexane) to afford **10b-tBDPS** (15 mg, 70%), which had the following spectral properties: $^{13}$C NMR ($CDCl_3$) $\delta$ 176.7, 146.1, 141.9, 141.8, 141.1, 139.1, 135.8, 135.7, 135.7, 135.2, 134.8, 133.5, 133.3, 129.9, 129.8, 129.7, 129.5, 128.0, 128.0, 127.9, 127.9, 127.7, 127.0, 126.0, 123.1, 122.1, 121.8, 121.2, 120.5, 116.5, 109.1, 87.1, 81.6, 54.7, 51.9, 38.0, 33.4, 29.0, 19.9; $^1$H NMR ($CDCl_3$) $\delta$ 9.38 (d, $J$ = 7.1, 1H), 7.72−7.68 (m, 5H), 7.57−7.33 (m, 11H), 7.18 (t, $J$ = 7.5, 1H) 6.41 (dd, $J$ = 7.4, 5.0, 1H), 5.20 (t, $J$ = 4.8, 1H), 4.63 (s, 2H), 4.42 (d, $J$ = 4.0, 1H), 3.05 (m, 1H), 2.92 (m, 1H), 2.70 (m, 1H), 2.55 (m, 1H), 1.40 (s, 9H); HRMS (*m*/*z*) for M + $H^+$ ($C_{41}H_{37}N_2O_2Si$), calcd 617.2617, obsd 617.2624.

**Preparation of Racemic (9*R*,12*S*,12a*S*)-*rel*-3,9,10,11,-12,12a-Hexahydro-9,12-epoxyindeno[1,2,3-*fg*]indolo[3,2,1-*kl*]pyrrolo[3,4-*i*][1]benzazocin-1-one (10a).** A solution of **10a-tBDPS** (98 mg) in THF (16 mL) was added to an aqueous solution (5.9 mL) of HF (0.175 mL of a 0.1 M aqueous solution) buffered with KF (35.3 mg). The solution was stirred for 24 h, taken up in DCM, and washed with aqueous $NaHCO_3$. The aqueous layer was extracted with DCM (3 × 100 mL), and the combined organic layers were immediately passed through a plug of $MgSO_4$ and evaporated to leave a residue that was triturated with 1:1 ether/hexane to afford **10a** (53 mg, 88%). The HPLC retention time and spectral data (NMR and MS) were identical to those obtained for the preparation of **10a** by the solid-phase method described above.

**Preparation of Racemic (9*S*,12*R*,12a*S*)-*rel*-3,9,10,11,-12,12a-Hexahydro-9,12-epoxyindeno[1,2,3-*fg*]indolo[3,2,1-*kl*]pyrrolo[3,4-*i*][1]benzazocin-1-one (10b).** Following the procedure for the preparation of **10a**, **10b-tBDPS** was desilyated as described above. Prior to acquiring the spectral data, partial isomerization to **10a** had occurred. Data for **10b**: $^1$H NMR (DMSO-$d_6$) $\delta$ 9.20 (d, $J$ = 7.5, 1H), 8.6 (s, 1H), 7.97 (d, $J$ = 7.7, 1H), 7.69 (d, $J$ = 8.2, 1H), 7.57 (d, $J$ = 7.3, 1H), 7.48 (t, $J$ = 7.3, 1H), 7.45−7.25 (m, 3H), 6.57 (m, 1H), 5.10 (m, 1H), 4.88 (s, 2H), 4.67 (m, 1H), 3.10 (m, 1H), 2.85 (m, 1H), 2.73 (m, 1H), 2.63 (m, 1H); MS (*m*/*z*) for M + Na ($C_{25}H_{18}N_2O_2Na$), calcd 401, obsd 401.

**Separation of the Enantiomers of 10a-tBDPS by Chiral HPLC and Preparation of both Enantiomers of 10a. 10a-tBDPS** was dissolved in a minimum amount of $CHCl_3$/EtOH (1:4), and aliquots (500 uL) were eluted off a chiralcel OD HPLC column (1 × 25 cm) with 100% EtOH at a flow rate of 1.5 mL/min. Fractions were collected and evaporated separately ($R_t$ for enantiomer A was 24−27 min, $R_t$ for enantiomer B was 36−39 min). Desilylation of each fraction was carried out as described above, and the individual products were purified by preparative HPLC as described for the preparation of **10a** via the solid-phase chemistry route. The HPLC retention times and MS spectral data of each enantiomer corresponded to authentic **10a**. Enantiomer A was obtained in 97% ee and enantiomer B was obtained in 90% ee as determined by analytical chiral HPLC using a chiralcel OD column (0.46 × 5 cm) eluted with 1:1 MeOH/EtOH at a flow rate of 0.25 mL/min ($R_t$ for enantiomer A was 14 min, $R_t$ for enantiomer B was 20.5 min).

**Computational Chemistry Methods.** Computational chemistry was performed using the SYBYL[21] software package running on a Silicon Graphic R4400 workstation. Molecular models of **10a** and **10b** were constructed by modifying the structure of staurosporin that was extracted from the Brookhaven Protein Databank (pdb code 1stc). Atoms corresponding to the glycoside portion of staurosporin were deleted, and the indole nitrogen (N12) of the resulting **4c** was modified to an $sp^3$ carbon to generate **4a**. Molecular models of **10a** and **10b** were constructed using standard bond lengths and bond angles of the SYBYL fragment library, and atoms types of the appropriate atoms were reassigned to the relevant types using the "type-only" option. Energy minimizations were realized with the SYBYL/MAXIMIN2 option by applying the conjugate gradient algorithm and setting a root-mean-square gradient of the forces acting on each atom to 0.05 kcal/mol as the convergence criterion. These SYBYL-minimized structures were subsequently subjected to full geometry optimizations in AM1 using double precision with the "precise" option and using the "mmok" command for the amide bond of the lactam.

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**Supporting Information Available:** Description of the HPLC method, $^1$H NMR and reversed-phase HPLC chromatograms for compounds **10b-TBDPS** and **11**−**13**, and chiral HPLC chromatograms for individual enantiomers of **10a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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