Intramolecular Friedel−Crafts-Type Reactions Involving *N*-Acyliminium Ions Derived from Glycine Templates

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Enantiomerically pure 4-substituted 2-aralkyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones (**1b**−**m**) in which the alkyl chain is $(CH_2)_n$, $n = 1-3$, behave as glycine templates giving by treatment with [hydroxy(tosyloxy)iodo]benzene in ethyl acetate *cis*-1-tosyloxy derivatives. When these compounds contain electron-rich aryl substituents with $n = 2$, they spontaneously cyclize through intramolecular Friedel−Crafts-type diastereoselective reactions to give penta- or hexacyclic compounds. Otherwise, they give by solvolysis *cis*-1-alkoxy derivatives, which in a second step, may be cyclized in acid if $n = 2$, 3. All these reactions must occur through *N*-acyliminium species in S_N1-like mechanisms. 1-Alkoxy-2-arylmethyl derivatives are reluctant to cyclize, giving *trans*-1-hydroxy compounds as the only isolated reaction products.

Introduction

N-Acyliminium ion-mediated carbon−carbon bond-forming reactions have found many applications, especially in cyclizations with π nucleophiles.[1,2] The *N*-acyliminium species are generated by acid treatment of *N*-(1-hydroxyalkyl)amides, which are frequently obtained by partial reduction[3] or addition of organometallics[4] to cyclic imides and, some times, by addition of amides or carbamates to aldehydes.[5] Access to *N*-(1-hydroxyalkyl)-amide precursors by oxidation is a less common methodology[6] that we have investigated in the case of 2,4-dimethyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (**1a**),[7] a system that contains three rings of the hexacyclic fungal metabolite *N*-acetylardeemin.[8] The pyrazino[2,1-*b*]quinazoline-3,6-dione structure is used by nature as a scaffold for constrained peptidomimetics that incorporate anthranilic acid as demonstrated by the isolation of other fungal metabolites such as glyantrypine,[9] fumiquinazolines,[10] and fiscalins.[11] Among other interesting biological properties displayed by these natural products, *N*-acetylardeemin reverses the multidrug resistance (MDR) to antitumor agents mediated by glycoprotein P-170,[12] an activity that is much retained in the above-mentioned tricyclic fragment[13] and moved us to study different synthetic approaches to this system.

In our previous work,[7] compound **1a** was easily oxidized to tosylate **3a** after treatment with the hypervalent iodine reagent [hydroxy(tosyloxy)iodo]benzene (**2**), which is commonly used for α-functionalization of ketones,[14] and the 1-hydroxy (**4a**) or 1-methoxy (**5a**) derivatives obtained by acid-catalyzed hydrolysis or methanolysis of **3a** reacted in acid media with electron-rich arenes to give 1-aryl derivatives **6a** as single diastereoisomers (Scheme 1).

The cis stereochemistry of all these compounds was supposed to be the result of S_N1-like mechanisms in which either the nucleophile attacks anti respect to the 4-methyl group of the *N*-acyliminium species **A** to give

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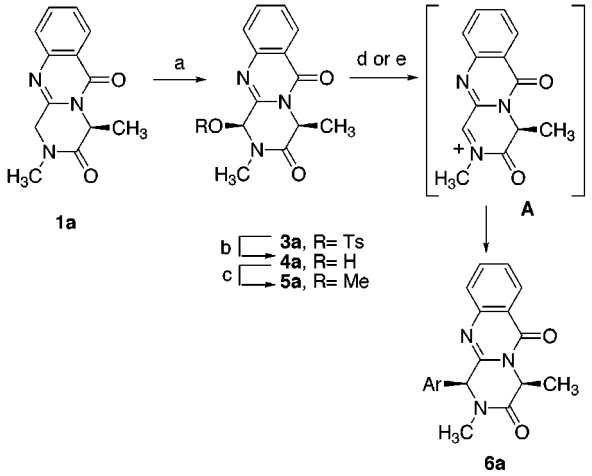
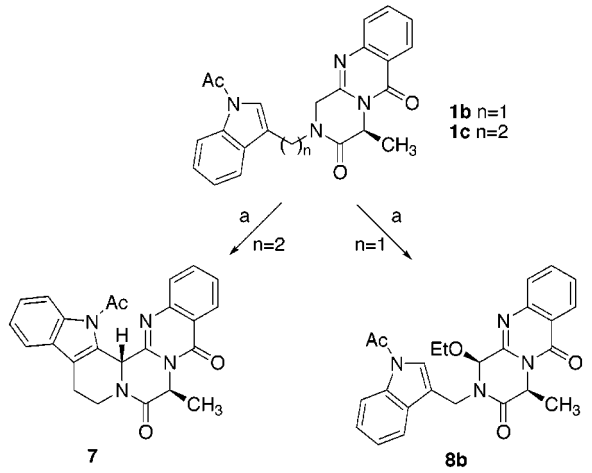
Scheme 1[a]



[a] Reagents and conditions: (a) **2**, EtOAc, reflux, 8 h; (b) H_2O, NH_4Cl; (c) *p*-TsOH (cat.), ROH, rt, 20 h; (d) (from **4a**) concd H_2SO_4, ArH, rt, 48 h; (e) (from **5a**) $BF_3{\cdot}Et_2O$ (1 equiv), ArH (4 equiv), rt, 24 h.

Scheme 2[a]



[a] Reagents and conditions: (a) **2**, EtOAc, reflux, 8 h.

the trans isomers, which equilibrate to the most stable cis isomers through enamine tautomers, or is the result of a kinetically preferred syn attack.

When this strategy was applied to intramolecular cyclizations looking for new synthetic entries to *N*-acetylardeemin analogues, and **1c** was used as the starting material,[15] compound **7** (Scheme 2) was directly obtained after treatment with **2**. However, **1b** gave in the same treatment compound **8b**.[16] No traces of the alternative isomers were observed in the reaction crudes.

Here we investigate in more detail these reactions and study their scope and stereochemistry by using representative *N*-aralkyl derivatives.

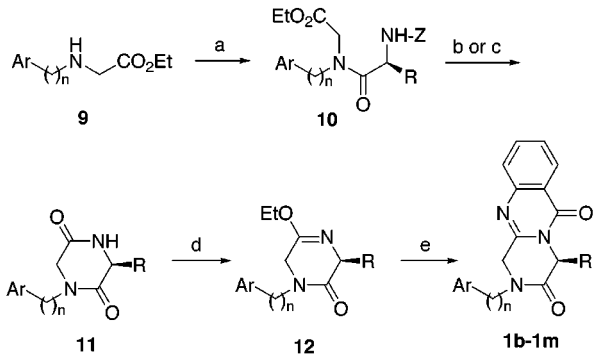
Results and Discussion

Synthesis of compounds **1b**−**m** (Table 1) was accomplished following a straightforward methodology[17] that starts with the condensation of ethyl *N*-aralkylglycinates **9** with L-Ala or L-Val to give the corresponding piperazine-2,5-diones **11** (Scheme 3). The required ethyl *N*-aralkylglycinates were prepared by reductive amination of the corresponding aldehyde with ethyl glycinate[18] or, alternatively, by *N*-alkylation of the corresponding aralkylamine with ethyl bromoacetate.[19] After activation of the unsubstituted amide function of compounds **11** to lactim ethers **12**, condensation with anthranilic acid afforded compounds **1b**−**m**.

Table 1. Structure of Compounds 1, 8, 15, and 16

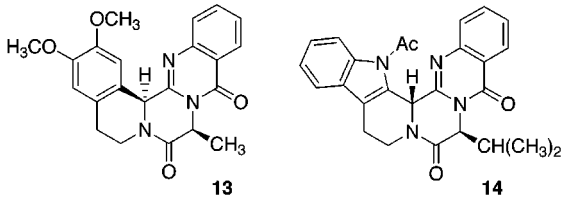
compd	Ar	n	R
b	1-acetyl-3-indolyl	1	CH_3 (*S*)
c	1-acetyl-3-indolyl	2	CH_3 (*S*)
d	C_6H_5	1	CH_3 (*S*)
e	4-$MeOC_6H_4$	1	CH_3 (*S*)
f	3,4-$(MeO)_2C_6H_3$	1	CH_3 (*S*)
g	2-naphthyl	1	CH_3 (*S*)
h	C_6H_5	2	CH_3 (*S*)
i	C_6H_5	2	CH_3 (*R*)
j	3,4-$(MeO)_2C_6H_3$	2	CH_3 (*S*)
k	C_6H_5	3	CH_3 (*S*)
l	C_6H_5	2	$CH(CH_3)_2$ (*S*)
m	1-acetyl-3-indolyl	2	$CH(CH_3)_2$ (*S*)

Scheme 3[a]



[a] Reagents and conditions: (a) Cbz(Boc)amino acid, EDC, CH_2Cl_2, rt, 24 h; (b) H_2/Pd−C, MeOH, 20 psi, rt, 3 h; (c) 200 °C, argon atmosphere; (d) $Et_3O{\cdot}BF_4$, CH_2Cl_2, Na_2CO_3, rt, 24 h; (e) anthranilic acid, 140 °C, 2 h.

Compounds **1j** and **1m** that, as well as **1c** have an electron-rich arene tethered by a ethylene chain, gave the cyclic compounds **13** (62%) and **14** (71%) as single diastereomers (NMR of the crude reaction product) after treatment with **2**.



All the remaining compounds **1**, which have less nucleophilic arenes and/or $n \neq 2$, gave the corresponding *cis*-1-ethoxy derivatives **8** in moderate to good yields when the crude products of the reaction with **2** were purified by column chromatography. Since compounds **8** were obtained in the same yields after exclusion of the

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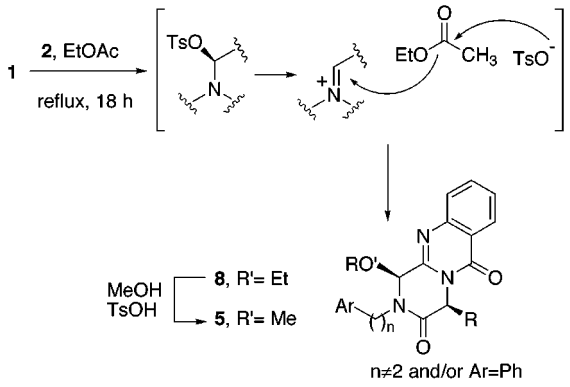
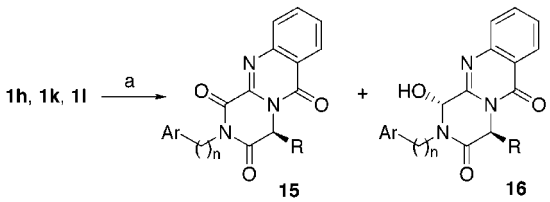
Scheme 4



Scheme 5[a]



Comp (yield %)

15h (25) + **16h** (42)

15k (47) + **16k** (20)

15l (52) + **16l** (0)

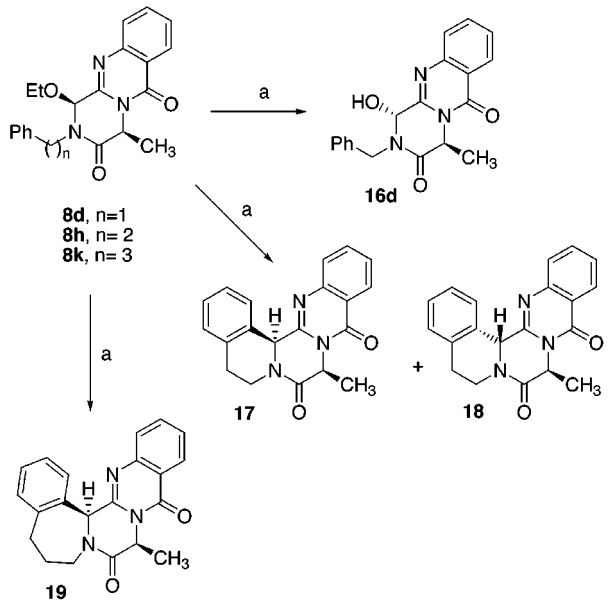
[a] Reagents and conditions: (a) (1) **2**, MeCN, 100 °C, 18 h; (2) NH_4Cl, H_2O/Cl_2CH_2, rt, 6 h.

possible traces of ethanol present in the solvent,[20] the ethoxy group of **8** must come from ethyl acetate itself (Scheme 4).

Thus, when some compounds (**1h**,**k**,**l**) were treated with **2** using acetonitrile as solvent, 1-oxo (compounds **15**) and *trans*-1-hydroxy (**16**) derivatives were the only reaction products after the reaction workup (Scheme 5). Similar oxidation compounds have been formed in other reactions with this system.[21] It is possible that compounds **15** are formed by dehydrogenation of the 1-oxo-11,11a-dihydro tautomers of compounds **16**.

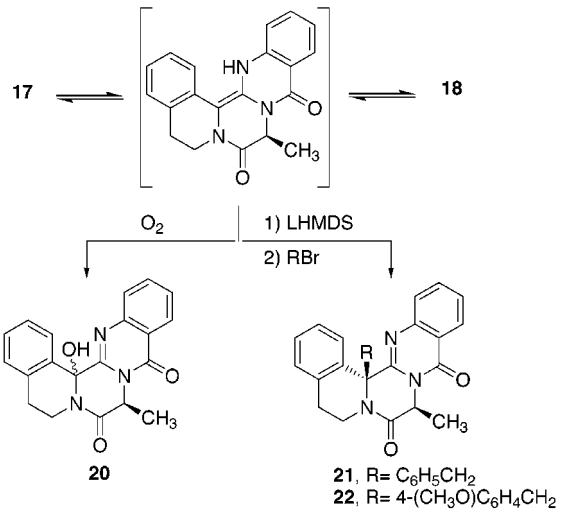
The above results prompted us to use 1-ethoxy compounds **8** as equivalents of glycine cations instead of the nonisolated tosyloxy intermediates. The reactivity of representative compounds in S_N1-type reactions was confirmed with **8d**,**g**−**i**,**l**; by using methanol as solvent in the presence of catalytic amounts of *p*-toluenesulfonic acid, the corresponding *cis*-1-methoxy derivatives **5** were obtained as single isomers in nearly quantitative yields (see Scheme 4). In the treatment of homologous series of compounds **8d**, **8h**, and **8k** (where Ar = Ph and n = 1, 2, and 3, respectively) with concentrate sulfuric acid at room temperature, compounds **16d** (a single isomer from **8d**) and **19** (a single isomer from **8k**) were obtained after workup with a large excess of water, while **8h** gave **17** and **18** as a 4:1 unseparable mixture. Lower amounts of water in the case of **8h** afforded the bisulfate of the isomer **17** as the only isolable compound (Scheme 6).

Scheme 6[a]



[a] Reagents and conditions: (a) (1) concd H_2SO_4, rt, 2 h; (2) ice−water.

Scheme 7



In solution, the mixture of isomers **17** and **18** must be in equilibrium through an easily oxidizable enamine form. In fact, when the evolution of a $CDCl_3$ solution of this mixture was followed by ^1H NMR, the 16b-hydroxy derivative **20** (Scheme 7) was isolated as the major product after 1 week. The same mixture generated an anion with lithium hexamethyldisilazide that was alkylated to give compounds **21** and **22** as single diastereomers. Their stereochemistry was unequivocally assigned by NOE experiments. Thus, a significant enhancement of the H-2′(6′) doublet (δ = 7.12 ppm) was observed in compound **22** after irradiation of the methyl protons (δ = 1.90 ppm). The syn attack of the anion derived from **17** and **18** contrasts to the kinetically favored anti attack previously observed in the anions derived from **1a**, **1d**, and other related tricyclic compounds, which is controlled by the 1,4-asymmetric induction of the pseudoaxial 4-methyl substituent.[22] These results are ascribable to a different conformation of the piperazine ring in the pentacyclic intermediate that must

(20) Ethyl acetate was refluxed for 4 h with acetic anhydride and some drops of concd H_2SO_4, distilled, dried with anhydrous K_2CO_3, filtered, and redistilled from CaH_2.

(21) Compounds **15** have been also formed in the attempted reductive (95% formic acid−C/Pd) or oxidative (DDQ) *N*(2)-debenzylation of the corresponding compounds **1**: Buenadicha, F. L.; Bartolomé, M. T.; Aguirre, M. J.; Avendaño, C.; Söllhuber, M. M. *Tetrahedron*: *Asymmetry* **1998**, *9*, 483−501.

place the methyl group pseudoequatorial being the α-face (anti attack) here prevented by the ethylene chain.

Several other attempts to cyclize compounds **8** in which $n=1$ also failed. For instance, treatment of **8e** and **8f** with catalytic amounts of *p*-toluenesulfonic acid in refluxing benzene gave the 1-hydroxy derivatives **16e** (54%) and **16f** (61%) as the only reaction products.

The cis or trans stereochemistry of all compounds, when indicated, was determined by conclusive NOE experiments, while their enantiomeric purity was confirmed by the absence of splitting of any signal in the ^{1}H NMR spectra after addition of Eu(hfc)$_3$ and by chiral HPLC for the starting materials.

In conclusion, acyliminium species directly formed from nonisolated 1-tosyloxy derivatives of compounds **1b**−**m** or by acid treatment of the corresponding 1-ethoxy derivatives **8** give intramolecular Friedel−Crafts-type reactions if the arene and the pyrazinoquinazoline portions are linked through di- or trimethylene chains. Otherwise, alkoxy or hydroxy derivatives are formed by nucleophilic attack of the solvents.

The frontal overlap of the orbitals involved in the S_N1-type reactions described here takes place preferentially by the upper (*β*) face of the cation, syn with respect to the C-4 substituent (see all compounds **8** and **5** as well as the cyclic compounds **13**, **17**, and **19**). Only in the case of important steric interactions, such as those imposed by the *N*-acetyl substituent in compounds **7** and **14**, does the aromatic ring interact with the lower (α) face of the cation, anti with respect to the C-4 substituent. The trans stereochemistry found in the 1-hydroxy derivatives **16** points to S_N2-type mechanisms.

Some representative compounds were studied as MDR reversal agents and as Ca^{2+} channel blockers and showed a moderate activity.[23]

Experimental Section

All reagents were of commercial quality and were used as received. Solvents were dried and purified using standard techniques. Reactions were monitored by TLC, on aluminum plates coated with silica gel with fluorescent indicator (Merck 60 F_{254}). Separations by flash chromatography were performed on silica gel (Merck 60, 230−400 mesh). Melting points were measured in open capillary tubes using a Reichert 723 hot-stage microscope and are uncorrected. IR spectra were obtained from films deposited on NaCl plates or from compressed KBr pellets for solid compounds. Unless otherwise noted, NMR spectra were recorded in $CDCl_3$ at 250 or 300 MHz for ^{1}H and at 63 or 75 MHz for ^{13}C (Servicio de Espectroscopía, Universidad Complutense). When necessary, assignments were aided by DEPT, COSY, and ^{13}C−^{1}H correlation experiments. Elemental analyses were determined by the Servicio de Microanálisis, Universidad Complutense. Optical rotations were measured at 25 °C on a 1 mL cell in $CHCl_3$ or MeOH at 589 nm, concentrations expressed in g/100 mL. Mass spectra (*m*/*e*) were obtained in the EI (70 eV) mode in Servicio de Espectroscopía U.C.M. HPLC analyses were performed using a Constametric 4100 system equipped with a chiral column (Chiracel OD) and UV−vis detector. Mobile phase: hexane/2-propanol (90:10).

Reactions of Compounds 1 with 2. General Procedure in EtOAc. A suspension of equimolar amounts of compounds **1** and **2** in EtOAc (25 mL) was refluxed for 18 h and then was allowed to reach rt. Solvent was removed under vacuum to leave a residue that was chromatographed on silica gel using EtOAc as eluent.

(7*S*,16b*R*)-16-Acetyl-7-methyl-10,11,16,16b-tetrahydro-7*H*-quinazolino[2′,3′:3,4]pyrazino[2,1-*a*]*β*-carboline-5,8-dione (7): 65% yield from **1c** (0.48 mmol); viscous oil; $[\alpha]^{25}_D = +84.0$ ($c = 0.10$, CH_2Cl_2); ^{1}H NMR δ 8.24 (d, 1H, $J = 8.0$ Hz), 7.74 (d, 1H, $J = 8.4$ Hz), 7.65−7.33 (m, 6H), 6.83 (s, 1H), 5.64 (q, 1H, $J = 7.4$ Hz), 4.87 (m, 1H), 3.10 (m, 1H), 2.90 (m, 1H), 2.85 (s, 3H), 2.70 (m, 1H), 1.77 (d, 3H, $J = 7.4$ Hz) ppm; ^{13}C NMR δ 169.1, 160.3, 149.1, 147.0, 137.6, 134.5, 130.3, 128.7, 128.2, 127.6, 127.4, 126.9, 125.2, 123.1, 119.6, 119.3, 113.9, 54.5, 52.9, 39.0, 27.0, 20.4, 16.0 ppm; IR 2934, 1680, 744 cm^{-1}; MS 412 (M^+), 369 (100), 355, 311, 185, 143, 130. Anal. Calcd for $C_{24}H_{20}N_4O_3$: C, 69.89; H, 4.89; N, 13.58. Found: C, 66.69; H, 4.56; N, 13.25.

(1*S*,4*S*)-1-Ethoxy-4-methyl-2-phenethyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (8h): 80% yield from **1h** (0,60 mmol); viscous oil; $[\alpha]^{25}_D = +70$ ($c = 0.12$, CH_2Cl_2); ^{1}H NMR δ 8.28 (d, 1H, $J = 8.0$ Hz) 7.80 (t, 1H, $J = 8.0$ Hz), 7.61 (d, 1H, $J = 8.0$ Hz), 7.51 (t, 1H, $J = 8.0$ Hz), 7.25−7.05 (m, 5H), 5.33 (q, 1H, $J = 7.1$ Hz), 5.13 (s, 1H), 4.15−4.05 (m, 1H), 3.68 (q, 2H, $J = 7.0$ Hz), 3.52−3.42 (m, 1H), 2.95 (t, 2H, $J = 7.5$ Hz), 1.77 (d, 3H, $J = 7.1$ Hz), 1.18 (t, 3H, $J = 7.0$ Hz) ppm; ^{13}C NMR δ 169.4, 160.2, 147.2, 147.0, 138.2, 134.8, 128.8, 128.7, 127.8, 127.6, 126.9, 126.8, 121.0, 87.9, 64.9, 53.1, 48.6, 34.7, 19.2, 15.1 ppm; IR 1684, 1609 cm^{-1}. Anal. Calcd for $C_{22}H_{23}N_3O_3$: C, 70.01; H, 6.14; N, 11.13. Found: C, 69.87; H, 6.30; N, 10.83.

(1*S*,4*S*)-1-Ethoxy-4-methyl-2-(3-phenylpropyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (8k): 48% yield from **1k** (0,17 mmol); viscous oil; $[\alpha]^{25}_D = +47.5$ ($c = 0.18$, CH_2Cl_2); ^{1}H NMR δ 8.27 (d, 1H, $J = 8.0$ Hz), 7.80 (m, 2H), 7.53 (t, 1H, $J = 7.0$ Hz), 7.23−7.00 (m, 5H), 5.20 (q, 1H, $J = 7.2$ Hz), 5.19 (s, 1H), 3.95−3.85 (m, 1H), 3.69 (q, 2H, $J = 7.0$ Hz), 3.40−3.30 (m, 1H), 2.66−2.56 (m, 2H), 2.05−1.96 (m, 2H), 1.76 (d, 3H, $J = 7.2$ Hz), 1.18 (t, 3H, $J = 7.0$ Hz) ppm; ^{13}C NMR δ 167.4, 167.1, 147.2, 147.0, 140.9, 134.9, 128.5, 128.3, 127.4, 127.0, 126.2, 120.7, 87.0, 64.8, 52.9, 45.7, 33.1, 29.3, 19.0, 14.9 ppm; IR 1685, 1608 cm^{-1}. Anal. Calcd for $C_{23}H_{25}N_3O_3$: C, 70.57; H, 6.44; N, 10.73. Found: C, 70.77; H, 5.94; N, 11.19.

(9*S*,16b*S*)-2,3-Dimethoxy-9-methyl-5,6,9,16b-tetrahydroisoquino[1′,2′:3,4]pyrazino[2,1-*b*]quinazoline-8,11-dione (13): 62% yield from **1j** (0.16 mmol); viscous oil; $[\alpha]^{25}_D = -11.6$ ($c = 0.40$, CH_2Cl_2); ^{1}H NMR δ 8.31 (d, 1H, $J = 7.7$ Hz), 7.85−7.74 (m, 2H), 7.53 (t, 1H, $J = 7.6$ Hz), 6.96 (s, 1H), 6.64 (s, 1H), 5.81 (s, 1H), 5.33 (q, 1H, $J = 7.1$ Hz), 4.74 (m, 1H), 3.83 (s, 3H), 3.66 (s, 3H), 3.37−3.14 (m, 2H), 2.74 (m, 1H), 1.16 (d, 3H, $J = 7.1$ Hz) ppm; ^{13}C NMR δ 168.8, 160.3, 149.1, 148.4, 147.5, 147.0, 1135.1, 127.6, 127.2, 127.1, 125.9, 125.1, 120.6, 112.5, 107.6, 60.9, 56.0, 56.0, 51.7, 42.6, 26.3, 19.0 ppm; IR 2931, 1678 cm^{-1}. MS *m*/*e* 391 (M^+, 100), 376, 348, 304, 262, 234, 190, 176, 130, 84, 77. Anal. Calcd for $C_{22}H_{21}N_3O_4$: C, 67.51; H, 5.41; N, 10.74. Found: C, 67.22; H, 5.43; N, 11.25.

(7*S*,16b*R*)- 16-Acetyl-7-isopropyl-10,11,16,16b-tetrahydro-7*H*-quinazolino[2′,3′:3,4]pyrazino[2,1-*a*]*β*-carboline-5,8-dione (14): 71% yield from **1m** (0.22 mmol); viscous oil; ^{1}H NMR δ 8.24 (d, 1H, $J = 8.0$ Hz), 7.75 (d, 1H, $J = 8.3$ Hz), 7.65−7.33 (m, 6H), 6.90 (s, 1H), 5.41 (d, 1H, $J = 9.9$ Hz), 4.87 (m, 1H), 3.15−3.02 (m, 1H), 2.93 (m, 1H), 2.86 (s, 3H), 2.70 (m, 1H), 2.45 (m, 1H), 1.30 (d, 3H, $J = 6.6$ Hz), 1,10 (d, 3H, $J = 6.6$ Hz) ppm; ^{13}C NMR δ 167.5, 160.3, 149.6, 146.7, 135.4, 134.0, 128.5, 128.2, 127.4, 127.0, 126.9, 124.8, 122.8, 120.3, 119.3, 118.8, 113.6, 61.6, 54.5, 38.4, 30.3, 29.5, 26.7, 20.1, 19.8 ppm; IR 1682 cm^{-1}. Anal. Calcd for $C_{26}H_{24}N_4O_3$: C, 70.89; H, 5.49; N, 12.72. Found: C, 70.56; H, 5.38; N, 13.03.

Reactions of 8 with Concentrated H_2SO_4. General Procedure. A solution of compounds **8** in concd H_2SO_4 (3 mL) was stirred at room temperature for 2 h. A mixture of ice−water was added, and then it was extracted with EtOAc. The combined organic layers were dried and concentrated, and the residue was chromatographed in silica gel with EtOAc/CH_2Cl_2 (1:1) as eluent.

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(23) Unpublished results.

(9*S*,16b*S*)-9-Methyl-5,6,9,16b-tetrahydroisoquino[1,2:3,4]pyrazino[2,1-*b*]quinazoline-8,11-dione bisulfate (17·H_2SO_4): 65% yield from **8h** (0.53 mmol); yellow solid; mp 194−196 °C; ^{1}H NMR (DMSO-d_6) δ 8.20 (d, 1H, J = 7.9 Hz), 7.92 (m, 1H), 7.80 (d, 1H, J = 8.0 Hz), 7.61 (m, 1H), 7.25−7.12 (m, 4H), 6.11 (s, 1H), 5.04 (q, 1H, J = 7.0 Hz), 4.42 (m, 1H), 3.50 (m, 1H), 3.14 (m, 1H), 2.93 (m, 1H), 0.94 (d, 3H, J = 7.0 Hz) ppm; ^{13}C NMR (DMSO-d_6) δ 167.6, 160.0, 147.9, 148.2, 135.0, 134.9, 134.0, 129.9, 128.1, 126.2, 123.5, 120.0, 59.4, 51.1, 40.7, 25.8, 18.1 ppm; IR 1670, 1608, 1600, 1589 cm^{-1}; MS 331 (100, M^+), 316, 288, 275, 201, 173, 130, 77. Anal. Calcd for $C_{20}H_{17}N_3O_2$. H_2SO_4: C, 55.94; H, 4.46; N, 9.78. Found: C, 55.51; H, 4.66; N, 9.64.

(10*S*,17b*S*)-10-Methyl-6,7,10,17b-tetrahydro-5*H*-benzo[3′,4′]azepino[2′,1′:3,4]pyrazino[2,1-*b*]quinazoline-9,12-dione (19): 53% yield from **8k** (0.15 mmol); oil; $[\alpha]^{25}_D$ = +53.6 (c = 0.27, CH_2Cl_2); ^{1}H NMR δ 8.34 (d, 1H, J = 7.8 Hz), 7.80 (m, 1H), 7.67 (d, 1H, J = 7.4 Hz), 7.54 (m, 1H), 7.25−6.60 (m, 4H), 5.91 (s, 1H), 5.35 (q, 1H, J = 7.1 Hz), 4.85 (m, 1H), 3.15−3.05 (m, 3H), 2.05−1.95 (m, 2H), 1.35 (d, 3H, J = 7.1 Hz) ppm; ^{13}C NMR δ 167.3, 160.0, 149.6, 147.1, 141.7, 138.1, 135.0, 131.2, 129.0, 137.6, 127.4, 127.1, 126.5, 126.4, 120.0, 64.4, 52.9, 49.0, 35.6, 27.0, 17.1 ppm; IR 1668, 1607, 1600, 1589 cm^{-1}. MS: 345 (100, M^+), 330, 316, 302, 288, 247, 201, 173, 144, 117, 91, 77. Anal. Calcd for $C_{21}H_{19}N_3O_2$: C, 73.03; H, 5.54; N, 12.17. Found: C, 73.20; H, 5.56; N, 12.58.

Alkylation Reactions of the Mixture 17 and 18. General Procedure. To a stirred solution of the mixture of **17** and **18** in anhyd THF (10 mL) at −78 °C under argon atmosphere was added LHMDS (1 equiv), and after 20 min, a solution of the corresponding benzyl halide in anhyd THF (5 mL) was also added. These conditions were kept for an additional 30 min, after which time the mixture was allowed to reach rt. After 4 h, the colorless solution was treated with saturated NH_4Cl solution and extracted with EtOAc. The organic layers were washed with water, dried, and concentrated to leave a residue that was chromatographed in silica gel using petroleum ether/EtOAc (1:1) as eluent.

(9*S*,16b*R*)-16b-Benzyl-9-methyl-5,6,9,16b-tetrahydroisoquino[1′,2′:3,4]pyrazino[2,1-*b*]quinazoline-8,11-dione (21): 44% yield; oil; ^{1}H NMR δ 8.24 (d, 1H, J = 8.3 Hz), 8,00 (t, 1H, J = 7.9 Hz), 7.66 (m, 2H), 7.50−7.00 (m, 9H), 5.20 (q, 1H, J = 7.0 Hz), 4.96 (dd, 1H, J = 13.5 Hz, 6.5 Hz), 4.32 (d, 1H, J = 15.2 Hz), 4.21 (d,1H, J = 15.2 Hz), 3.75 (td, 1H, J = 13.5 Hz, 5.2 Hz), 3.30 (m, 1H), 2.90 (m, 1H), 1.12 (d, 3H, J = 7.0 Hz) ppm; ^{13}C NMR δ 169.1, 160.4, 151.4, 149.5, 146.4, 138.3, 135.8, 134.9, 133.2, 130.5, 129.8, 128.8, 128.4, 127.8, 127.6, 127.1, 126.9, 126.7, 125.8, 120.3, 67.3, 50.8, 47.5, 37.9, 27.2, 1.8 ppm; IR 1680, 1600, 1514 cm^{-1}. Anal. Calcd for $C_{27}H_{23}N_3O_2$: C, 76.94; H, 5.50; N, 9.97. Found: C, 77.22; H, 5.83; N, 9.59.

(9*S*,16b*R*)-16b-(4-Methoxybenzyl)-9-methyl-5,6,9,16b-tetrahydroisoquino[1′,2′:3,4]pyrazino[2,1-*b*]quinazoline-8,11-dione (22): 57% yield; oil; ^{1}H NMR δ 8,22 (d, 1H, J = 7.5 Hz), 8.00 (m, 1H), 7.66 (m, 1H), 7.50−7.15 (m, 5H), 7.12 (d, 2H, J = 8,6 Hz), 6.85 (d, 2H, J = 8.6 Hz), 5.51 (q, 1H, J = 7.1 Hz), 4.96 (m, 1H), 4.32 (d, 1H, J = 9.5 Hz), 4.21 (d, 1H, J = 9.5 Hz), 3.77 (s, 3H), 3.20−3.80 (m, 2H), 2.89 (m, 1H), 1.90 (d, 3H, J = 7.1 Hz) ppm; ^{13}C NMR δ 171.3, 161.0, 158.0, 151.0, 146.4, 137.2, 134.3, 132.8, 130.2, 129.5, 129.3, 128.8, 128.3, 128.0, 127.7, 114.1, 66.0, 55.3, 54.2, 52.4, 40.3, 29.3, 17.9 ppm; IR 1680, 1513 cm^{-1}. Anal. Calcd for $C_{28}H_{25}N_3O_3$: C, 74.48; H, 5.58; N, 9.31. Found: C, 73.95; H, 5.43; N, 9.25.

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Supporting Information Available: Complete spectroscopic and analytical data of compounds **8b**,**d**−**g**,**i**,**l**, **15**, **16**, and **20**. A description of compounds **1** and their precursors is available upon request. This material is available free of charge via the Internet at http://pubs.acs.org.

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