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TETRAHEDRON: *ASYMMETRY*

On the fate of the tryptophan stereocenter during the synthesis of hexacyclic analogues of *N*-acetylardeemin

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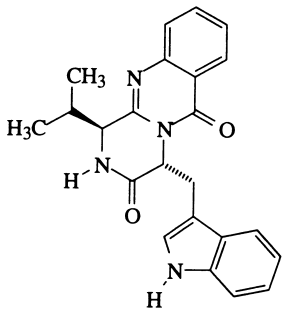
Abstract

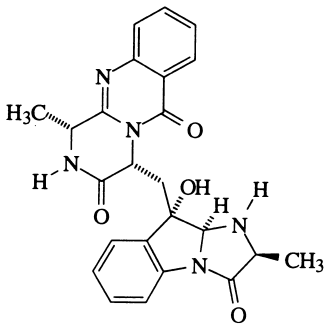
The reaction between 6-acetyl-3-alkyl-1-ethoxy-3,4,5a,6,11,11a-hexahydro-10b*H*-pyrazino-[2′,1′-5,1]pyrrolo-[2,3-*b*]indole-1,4-diones and anthranilic acid was studied from a stereochemical point of view. Various degrees of epimerization of the tryptophan and alanine stereocenters were observed in compounds with a *cis* relationship between their H-3 and H-11a hydrogen atoms, and stereochemistry was retained in the *trans* compounds. These observations are explained in terms of steric compression between the C_5=O, C_7–alkyl and C_8=O groups in the hexacyclic reaction products. Acylation at N-2 with *o*-azidobenzoyl chloride followed by an intramolecular aza Wittig reaction afforded the target 10-acetyl-5,7,8,9a,10,14b,15,15a-octahydroindolo[3′′,2′′-4′,5′]pyrrolo[2′,1′-3,4]pyrazino[2,1-*b*]quinazoline-5,8-diones with retention of all stereocenters.

1. Introduction

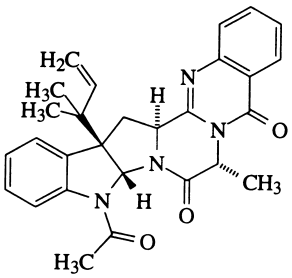
The pyrazino[2,1-*b*]quinazoline structure is present in several families of natural products, like the fiscalins[1] and the fumiquinazolines,[2] and also in *N*-acetylardeemin.[3] The latter compound is one of the most potent known inhibitors of multi-drug resistance to antitumor agents (MDR).[4]



Fiscalin B



Fumiquinazoline A



N-Acetylardeemin

The synthesis of the pyrazino[2,1-*b*]quinazoline ring system can be achieved by a number of methods.[5] One of simplest consists of the reaction of iminoethers derived from 2,5-piperazinediones with anthranilic

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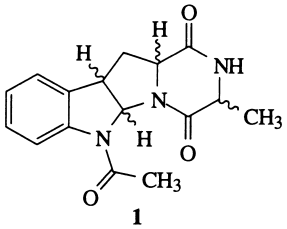
acid.[6] However, this reaction has received little attention from the stereochemical point of view in spite of its potential in natural product synthesis. As part of our studies on the synthesis of *N*-acetylardeemin analogues as potential MDR inhibitors,[7] we became interested in studying the stereochemistry of the condensation between pyrazino[2′,1′-5,1]pyrrolo[2,3-*b*]indole-1,4-dione derivatives **1**[8] and anthranilic acid. We report here the fate of the stereogenic centers during this transformation.



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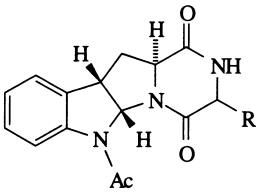
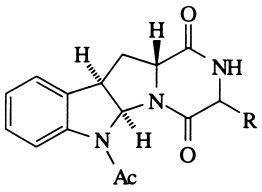
2. Results and discussion

As shown in Scheme 1, the synthesis of compounds **1a** and **b** was initiated by preparation of Boc-protected dipeptides **2** from L-tryptophan methyl ester and the suitable protected amino acid. Tandem deprotection–cyclization of compounds **2** under thermal conditions afforded diketopiperazines **3**. These were cyclized in the presence of acid[8–10] to compounds **4**, which were finally acetylated at the indoline nitrogen in order to increase their stability,[11] yielding compounds **1a** and **b**. In the case of glycine derivative **4a**, the acetylation reaction yielded two additional products, which were identified as the diacetylated derivative **5** and the acetylated diketopiperazine **6**.

Compounds **1c**–**f** were prepared from L- and D-alamine and L- and D-tryptophan by a similar method, as previously described by us.[8]

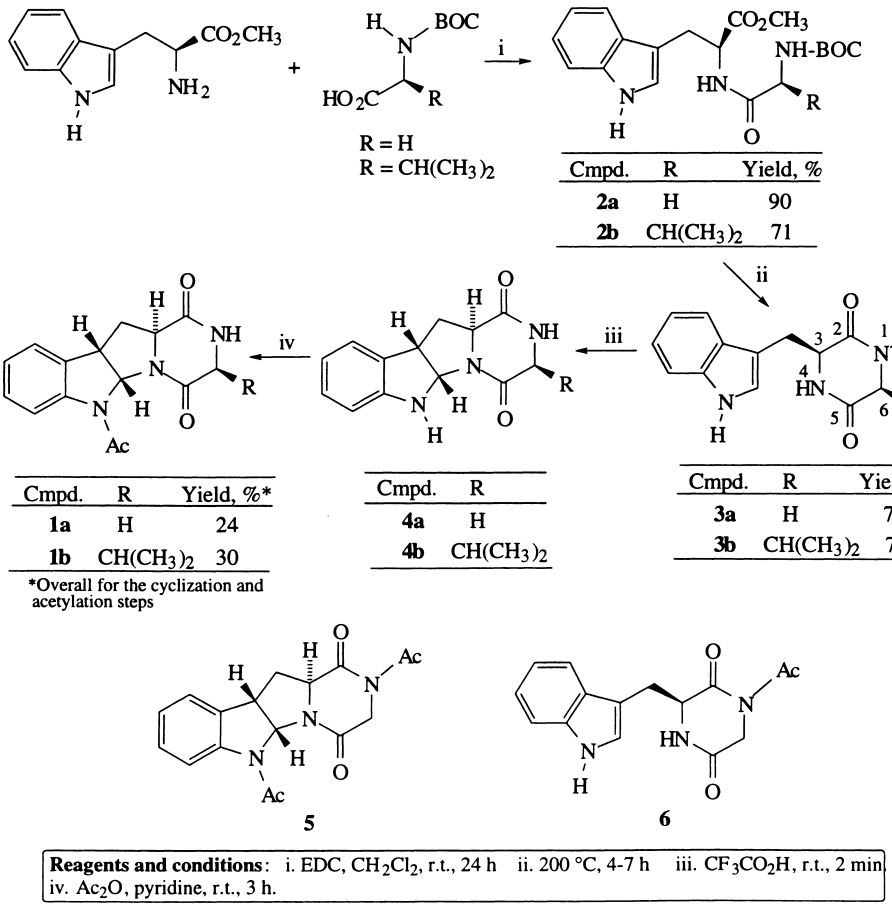


1c R = (*S*) Me
1d R = (*R*) Me



1e (*ent*-**1d**) R = (*S*) Me
1f (*ent*-**1c**) R = (*R*) Me

To our knowledge, the only literature precedent to the reaction under study is due to Rajappa and Advani,[6a] who investigated the reactions between anthranilic acid and the iminoethers derived from *cyclo*-(L-Pro-Gly), *cyclo*-(L-Pro-L-Val) and *cyclo*-(L-Pro-D-Val). In the first case, they observed racemization of the proline stereogenic center, a behavior that can be attributed to acid-catalyzed tautomerism to yield an achiral enamine **I**, which upon protonation reverts with equal probability to the *R* or *S* enantiomer of the starting compound.



Cmpd.	R	Yield, %
2a	H	90
2b	$CH(CH_3)_2$	71

Cmpd.	R	Yield, %*
1a	H	24
1b	$CH(CH_3)_2$	30

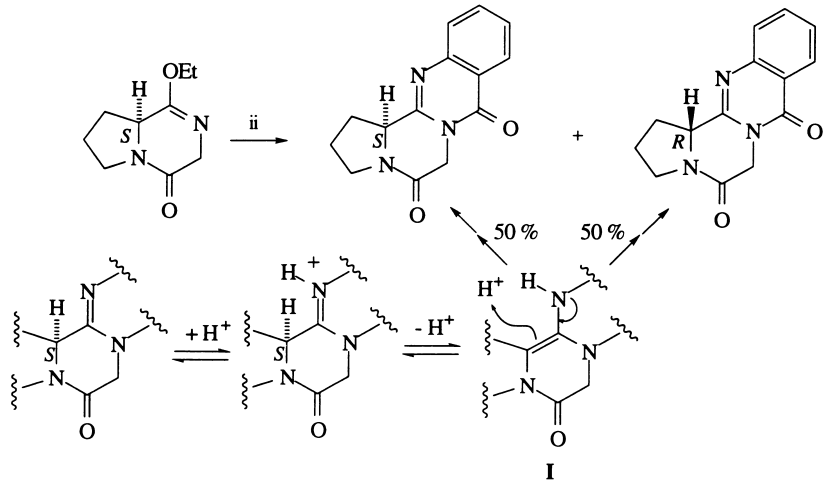
*Overall for the cyclization and acetylation steps

Cmpd.	R
4a	H
4b	$CH(CH_3)_2$

Cmpd.	R	Yield, %
3a	H	73
3b	$CH(CH_3)_2$	70

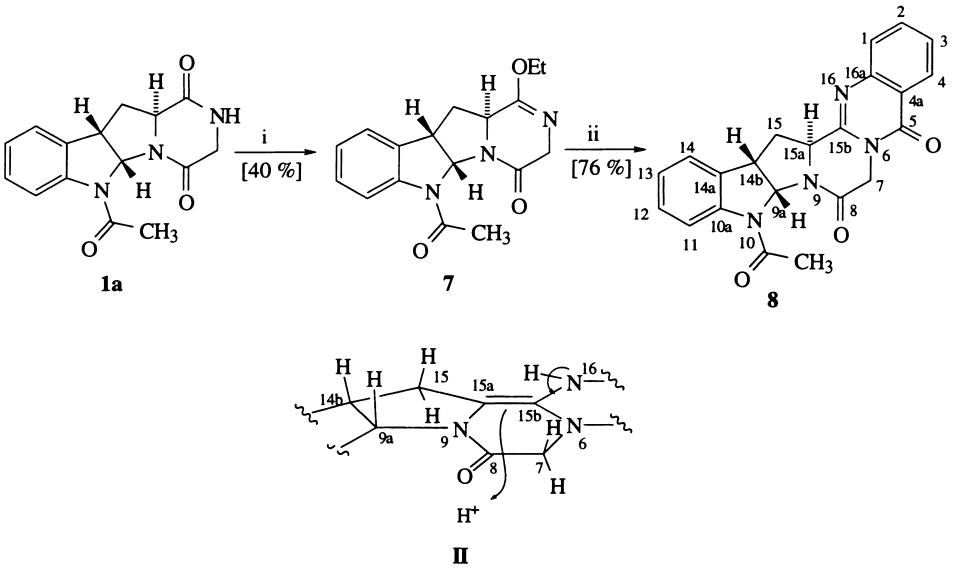
Reagents and conditions: i. EDC, CH_2Cl_2, r.t., 24 h ii. 200 °C, 4-7 h iii. CF_3CO_2H, r.t., 2 min iv. Ac_2O, pyridine, r.t., 3 h.

Scheme 1.



We considered it of interest to examine a similar reaction of compound **1a**, since it would allow the racemization of the derived tryptophan C-15a position on a chiral substrate to be studied. The structure of enamine **II**, the analogue of intermediate **I** depicted above, suggests that protonation from the bottom face avoids interaction with the H-9a, H-14b and H-15 pseudoaxial protons, and should therefore be favored, leading to retention of the *S* configuration at the tryptophan stereocenter. Iminoether **7** was obtained from

compound **1a** by treatment with triethyloxonium tetrafluoroborate in the presence of sodium carbonate.[12] When this compound was melted with neat anthranilic acid at 140°C for 4 h, it afforded **8** as the only reaction product in 76% yield (Scheme 2), confirming the stereoselective protonation of intermediate **II**.

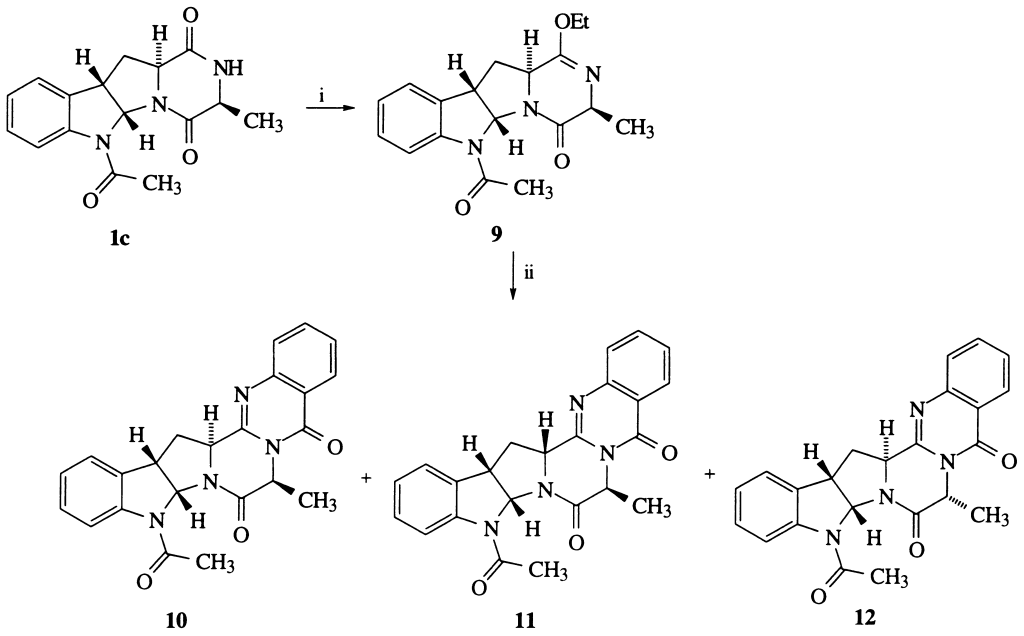


Scheme 2.

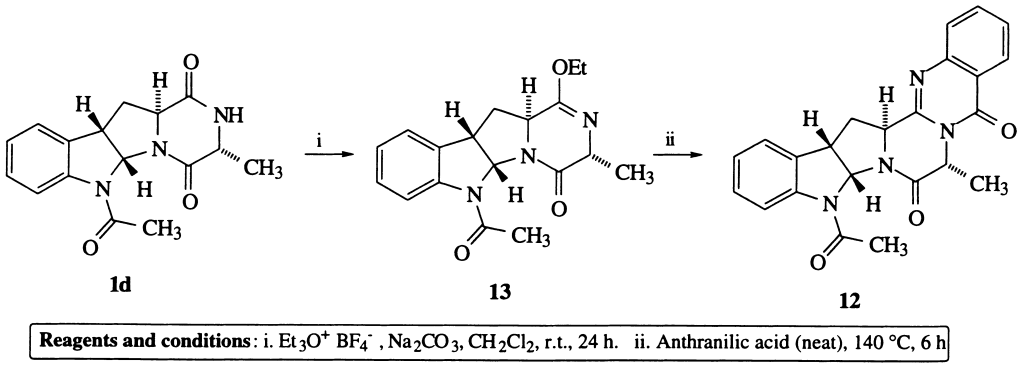
On the basis of our previous observations on the behavior of 2-acyl derivatives of structures **1**,[8] we predicted the possibility that the interactions between the substituents at the C-7 position and the C-5 carbonyl might exert an influence on the epimerization of the tryptophan stereocenter. Indeed, as shown in Scheme 3, transformation of compound **1c** into the corresponding iminoether **9** followed by reaction with anthranilic acid afforded a mixture of three hexacyclic derivatives, where the major product (compound **10**, 23%) retained the configuration of all stereocenters, while compounds **11** (8%) and **12** (3%) showed epimerization at the tryptophan and alanine stereocenters, respectively. On the other hand, iminoether **13**, with an *R* configuration at the alanine stereocenter and obtained from compound **1d**, gave exclusively the hexacyclic derivative **12** upon treatment with anthranilic acid, with retention of the stereochemistry (Scheme 4).

In order to increase the structural variation for biological studies, we carried out the reactions of iminoethers **14** and **16** with anthranilic acid. As expected, they behaved in the same way as their enantiomers (**13** and **9**, respectively), since compound **14** led to **15** (38%) as the only product, with retention of the stereochemistry (Scheme 5), while **16** afforded a mixture of **17** (20%), **18** (13%) and **15** (4%) (Scheme 6).

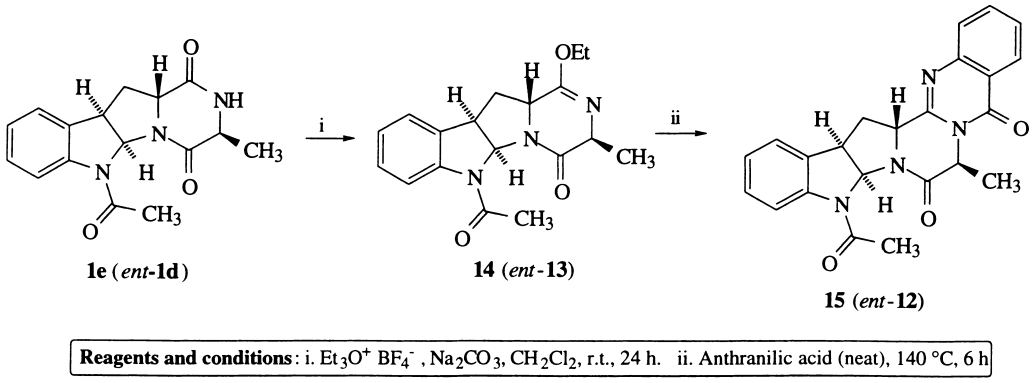
The easier epimerization of compound **10** with respect to **12** can be ascribed to the steric compression between the C-5 and C-8 carbonyls and the C-7 methyl group, which is relieved by epimerization at C-15a or at C-7.[13] This effect is absent in compound **12**, which explains its tendency to retain the configuration of its stereocenters.



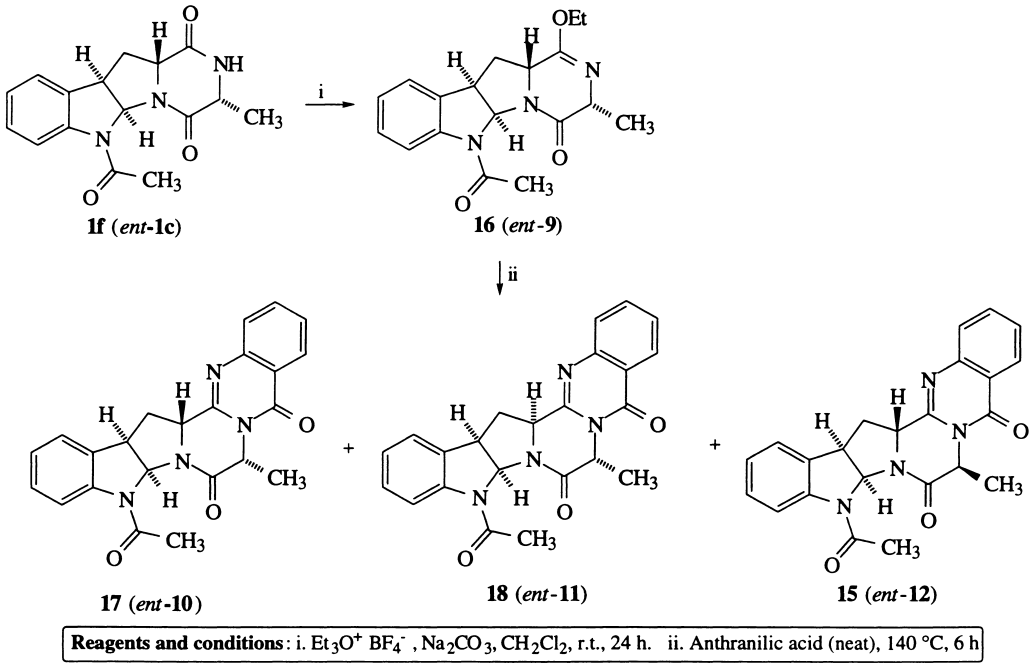
Scheme 3.



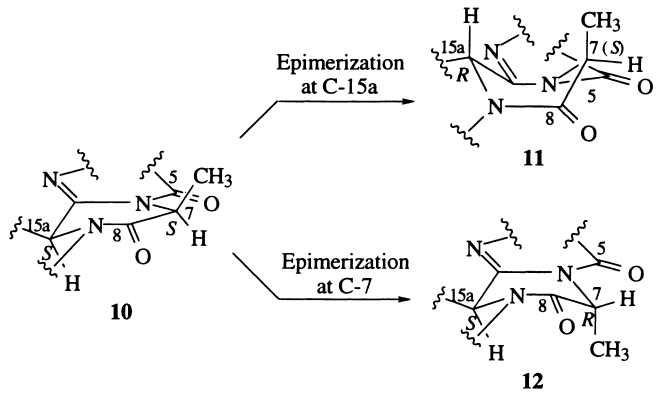
Scheme 4.



Scheme 5.



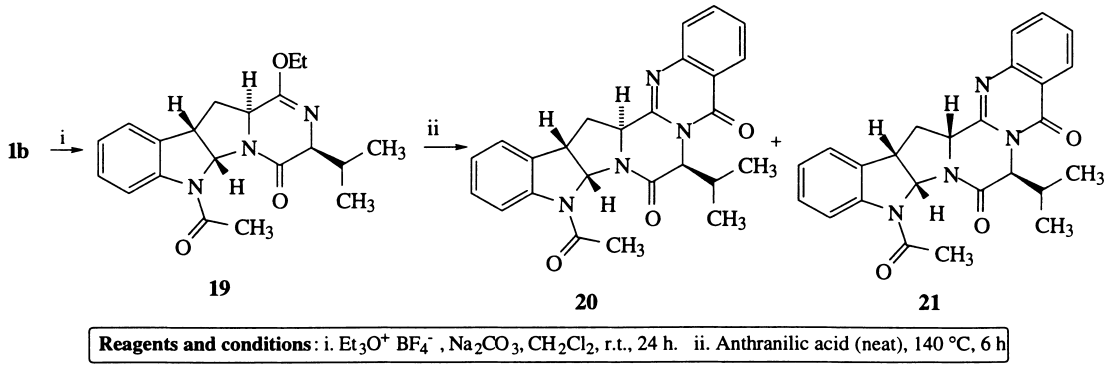
Scheme 6.



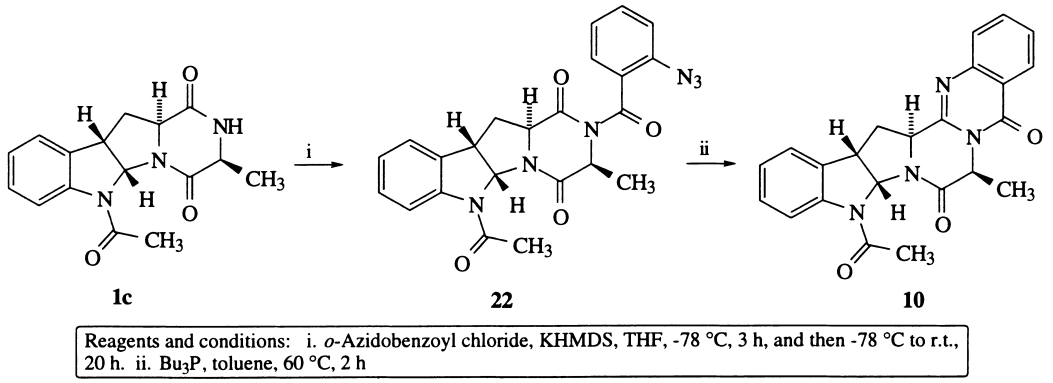
According to this explanation, the presence of groups bulkier than methyl at C-7 should lead to an increased tendency to epimerization. This assumption was checked by submitting iminoether **19**, derived from the valine derivative **1b**, to our usual conditions for reaction with anthranilic acid. The major product (45%) was compound **21**, epimerized at the tryptophan stereocenter, with only minor amounts (14%) of compound **20** (Scheme 7).[14]

Finally, we decided to examine the possibility of preparing the target hexacyclic compounds without epimerization. Since work by others[3b] and by ourselves[8] shows the possibility of acylating derivatives of the tetracyclic pyrazino[2′,1′-5,1]pyrrolo[2,3-*b*]indole-1,4-dione systems with retention of the stereochemistry by use of hindered bases, we treated compound **1c** with *o*-azidobenzoyl chloride in the presence of KHMDS at −78°C, and obtained **22** as a single diastereoisomer in 54% yield. An intramolecular aza Wittig reaction of **22** afforded compound **10** in 81% yield and as a single stereoisomer (Scheme 8).

Stereochemical assignments were based upon NOE experiments, which are summarized in Fig. 1.



Scheme 7.



Scheme 8.

3. Experimental

All reagents were of commercial quality (Aldrich, Fluka, SDS, Probus) and were used as received. Solvents (SDS, Scharlau) were dried and purified using standard techniques. The expression 'petroleum ether' refers to the fraction boiling at 40–60°C. Reactions were monitored by thin layer chromatography, on aluminum plates coated with silica gel with fluorescent indicator (Macherey–Nagel Alugram Sil G/UV_{254}). Catalytic hydrogenations were carried out using a Parr 3920 shaking reactor. Separations by flash chromatography were performed on silica gel (SDS 60 ACC, 230–400 mesh). Melting points were measured on a Reichert 723 hot stage microsope, and are uncorrected. Infrared spectra were recorded on Buck Scientific 500 and Perkin–Elmer Paragon 1000 FT-IR spectrophotometers, with solid compounds compressed into KBr pellets and liquid compounds placed between two NaCl disks. NMR spectra were obtained on a Bruker AC-250 spectrometer (250 MHz for ^1H, 63 MHz for ^{13}C) spectrometer (Servicio de Espectroscopía, Universidad Complutense), with $CDCl_3$ or d_6-DMSO as solvents. When necessary, assignments were aided by DEPT, COSY and ^{13}C–^1H correlation experiments. Optical rotations were determined at 25°C on a 1 ml cell, using a Perkin–Elmer 240 polarimeter operating at the emission wavelength of a sodium lamp; concentrations are given in g/100 ml. Elemental analyses were determined by the Servicio de Microanálisis, Universidad Complutense, on a Perkin–Elmer 2400 CHN microanalyzer.

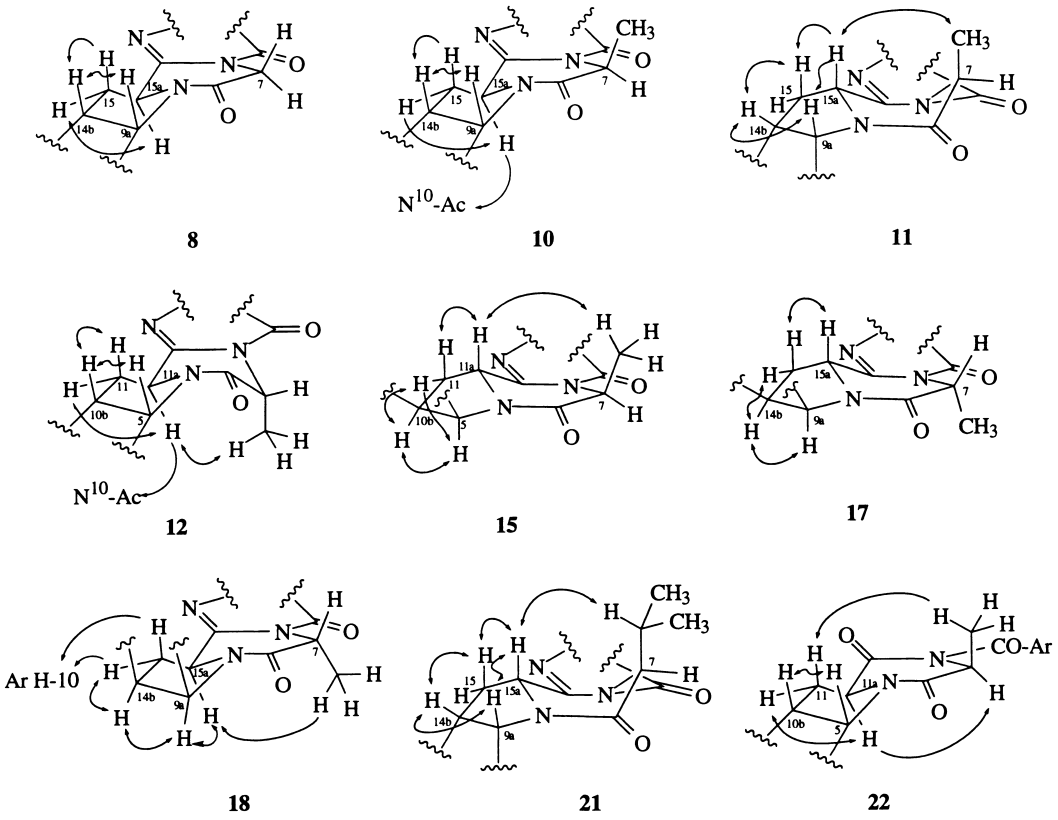


Fig. 1.

3.1. *Methyl* N-*(*tert-*butyloxycarbonyl)glycyl tryptophanate (**2a**)*

To a solution of tryptophan methyl ester (1 g, 4.6 mmol) in dry dichloromethane (50 ml) was added *N*-Boc-glycine (0.88 g, 4.6 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (0.88 g, 4.6 mmol), under an argon atmosphere. The reaction was protected from light and stirred at room temperature for 24 h. The solution was washed with 1 N aqueous HCl (7 ml) and 1 N aqueous $NaHCO_3$ (7 ml). The residue was chromatographed on silica gel, eluting with ethyl acetate, yielding the dipeptide **2a** (1.55 g, 90%) as an off-white solid. Mp, 55°C. IR (KBr): 3334.7 (NH), 1672.9 (CO_2CH_3 and CO–N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.63 (br. s, 1H, NH^i); 7.49 (d, 1H, *J*=7.5, H-4′); 7.31 (d, 1H, *J*=7.5, H-7′); 7.12 (m, 2H, H-5′, 6′); 6.94 (d, 1H, *J*=2.2 Hz, H-2′); 6.79 (d, 1H, *J*=7.4, NH); 5.26 (br. s, 1H, NH); 4.90 (m, 1H, Hα-Trp); 3.71 (d, 2H, *J*=4.4 Hz, Hα-Gly); 3.63 (s, 3H, CO_2CH_3); 3.29 (d, 2H, *J*=5.3, Hβ-Trp); 1.42 (s, 9H, Boc). ^{13}C-NMR ($CDCl_3$) δ: 172.34 (CO_2CH_3); 169.47 (CO–Gly); 156.19 ($CO_2C(CH_3)_3$); 136.23 (C-7′a); 127.54 (C-3′a); 123.32 (C-2′); 122.20 (C-4′); 119.64 (C-5′); 118.39 (C-6′); 111.55 (C-7′); 109.46 (C-3′); 80.30 ($CO_2C(CH_3)_3$); 52.97 (Cα-Trp); 52.56 (CO_2CH_3); 44.17 (Cα-Gly); 28.37 ($CO_2C(CH_3)_3$); 27.62 (Cβ-Trp) ppm. $[\alpha]_D^{25}$=+40.8 (c 0.50, $CHCl_3$). Anal. calcd for $C_{19}H_{25}N_3O_5$: C, 60.80; H, 6.67; N, 11.20. Found: C, 60.30; H, 6.29; N, 10.92.

3.2. *Methyl* N-*(*tert-*butyloxycarbonyl)*-L-*valyl tryptophanate (**2b**)*

To a solution of tryptophan methyl ester (1.5 g, 6.9 mmol) in dry dichloromethane (50 ml) was added *N*-Boc-L-valine (1.30 g, 6.9 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (1.32 g,

6.9 mmol), under an argon atmosphere. The reaction and purification were carried out as in the synthesis of **1a**, yielding the dipeptide **2b** (2.03 g, 71%) as an off-white solid. Mp, 136–138°C. IR (KBr): 3324.2 (NH), 1659.3 (CO_2CH_3 and CO–N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.14 (br. s, 1H, NH^i); 7.51 (d, 1H, *J*=7.6, H-4′); 7.33 (d, 1H, *J*=7.7, H-7′); 7.14 (m, 2H, H-5′, 6′); 7.02 (d, 1H, *J*=2.1 Hz, H-2′); 6.74 (d, 1H, *J*=7.6, NH); 5.03 (d, 1H, *J*=8.4 Hz, NH); 4.90 (m, 1H, Hα-Trp); 3.90 (m, 1H, Hα-Val); 3.64 (s, 3H, CO_2CH_3); 3.29 (m, 2H, Hβ-Trp); 2.06 (m, 1H, C*H*$(CH_3)_2$); 1.41 (s, 9H, Boc); 0.89 and 0.82 (2d, *J*=6.8 Hz, CH(C*H*$_3)_2$). ^{13}C-NMR ($CDCl_3$) δ: 172.10 (*C*O_2CH_3); 171.44 (CO–Val); 155.84 (*C*$O_2C(CH_3)_3$); 136.14 (C-7′a); 127.43 (C-3′a); 123.13 (C-2′); 122.16 (C-4′); 119.61 (C-5′); 118.42 (C-6′); 111.35 (C-7′); 109.51 (C-3′); 79.82 ($CO_2C(CH_3)_3$); 59.69 (Cα-Val); 52.79 (Cα-Trp); 52.34 (CO_2CH_3); 31.14 (*C*H$(CH_3)_2$); 28.28 ($CO_2C(CH_3)_3$); 27.61 (Cβ-Trp); 19.10 and 17.54 (CH(*C*H$_3)_2$) ppm. $[\alpha]_D^{25}$=+51.6 (c 0.50, $CHCl_3$). Anal. calcd for $C_{22}H_{31}N_3O_5$: C, 63.31; H, 7.43; N, 10.07. Found: C, 63.73; H, 7.33; N, 9.88.

*3.3. (3S)-3-(3-Indolylmethyl)-2,5-piperazinedione (**3a**)*

Compoud **2a** (1.92 g, 5.12 mmol) was heated at 200°C under a stream of argon for 4 h. The off-white residue was identified as compound **3a**. Yield, 0.9 g (73%). Mp, 300–301°C. IR (KBr): 3337.6, 3215.5 (NH); 1668.0 (CO–NH). ^{1}H-NMR (d_6-DMSO) δ: 10.94 (br. s, 1H, NH^i); 8.13 (d, 1H, *J*=2.3 Hz, NH); 7.79 (s, 1H, NH); 7.55 (d, 1H, *J*=7.8, H-4′); 7.33 (d, 1H, *J*=8.0, H-7′); 7.00 (m, 3H, H-2′, 5′, 6′); 4.02 (m, 1H, H-3); 3.30 (dd, 1H, *J*=17.2 and 2.8 Hz, H-6); 3.24 (m, 1H, Hβ-Trp); 3.01 (dd, 1H, *J*=14.4 and 4.6 Hz, Hβ-Trp); 2.77 (d, 1H, *J*=17.2, H-6) ppm. ^{13}C-NMR (d_6-DMSO) δ: 167.92 and 165.95 (2CO); 135.87 (C-7′a); 127.43 (C-3′a); 124.55 (C-2′); 120.85 (C-4′); 118.64 (C-5′); 118.39 (C-6′); 111.13 (C-7′); 108.28 (C-3′); 55.39 (C-3); 43.78 (C-6); 29.13 (CH_2) ppm. $[\alpha]_D^{25}$=+43.2 (c 0.25, DMSO). Anal. calcd for $C_{13}H_{13}N_3O_2$: C, 64.20; H, 5.35; N, 17.28. Found: C, 63.82; H, 5.32; N, 16.92.

*3.4. (3S,6S)-3-(3-Indolylmethyl)-6-isopropyl-2,5-piperazinedione (**3b**)*

Compoud **2b** (2.03 g, 4.9 mmol) was heated at 200°C under a stream of argon for 7 h. The off-white residue was identified as compound **3b**. Yield, 1.52 g (75%). Mp, 215–217°C. IR (KBr): 3333.6, 3198.7 (NH); 1668.1 (CO–NH). ^{1}H-NMR (d_6-DMSO) δ: 10.87 (br. s, 1H, NH^i); 8.02 (s, 1H, NH); 7.90 (s, 1H, NH); 7.59 (d, 1H, *J*=7.7, H-4′); 7.28 (d, 1H, *J*=7.9, H-7′); 7.07 (s, 1H, H-2′); 6.98 (m, 2H, H-5′, 6′); 4.14 (br. s, 1H, H-3); 3.48 (br. s, 1H, H-6); 3.22 (dd, 1H, *J*=14.3 and 4.7 Hz, Hβ-Trp); 3.06 (dd, 1H *J*=14.4 and 4.4 Hz, Hβ-Trp); 1.63 (m, 1H, C*H*$(CH_3)_2$); 0.59 and 0.15 (2 d, 6H, *J*=6.9 Hz, CH(C*H*$_3)_2$) ppm. ^{13}C-NMR (d_6-DMSO) δ: 167.33 and 166.24 (2CO); 135.96 (C-7′a); 127.88 (C-3′a); 124.44 (C-2′); 120.61 (C-4′); 118.85 (C-5′); 118.12 (C-6′); 110.95 (C-7′); 108.74 (C-3′); 59.22 (C-6); 55.12 (C-3); 31.04 (*C*H$(CH_3)_2$); 18.27 and 16.01 (CH(*C*H$_3)_2$) ppm. $[\alpha]_D^{25}$=−63.6 (c 0.55, DMSO). Anal. calcd for $C_{16}H_{19}N_3O_2$: C, 67.37; H, 6.67; N, 14.74. Found: C, 67.01; H, 6.37; N, 14.37.

*3.5. (5aR,10bS,11aS)-6-Acetyl-1,3,4,5a,6,10b,11,11a-octahydro-2H-pyrazino[2′,1′-5,1]-pyrrolo[2,3-b]indole-1,4-dione (**1a**)*

Compound **3a** (800 mg, 2.1 mmol) was added in one portion to trifluoroacetic acid (10 ml). The suspension was stirred until complete disolution (ca. 2 min), and was poured onto a vigorously stirred biphasic system of dichloromethane (40 ml) and 20% aqueous potassium carbonate (40 ml), externally cooled with an ice bath. The pH of the aqueous layer was adjusted to 8 and it was extracted with dichloromethane (20×10 ml). The combined organic layers were dried over anhydrous sodium sulfate

and evaporated. The residue was examined by ^{1}H-NMR and identified as compound **4a**, and was used for the next step without further purification.

A solution of the crude compound **4a** (539 mg, 1.44 mmol) in pyridine (8 ml) and acetic anhydride (2.34 ml) was stirred at room temperature for 3 h. The solution was diluted with dichloromethane (10 ml) and filtered to remove compound **3a** (191 mg, 42%), from ring opening of the starting material. The filtrate was evaporated, and the residue was diluted with dichloromethane (10 ml) and washed with water (10 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed on silica gel, eluting with ethyl acetate, yielding 150 mg (24%) of compound **1a**, 30 mg (4%) of 2,6-diacetylpyrazino[2′,1′-5,1]pyrrolo[2,3-*b*]indole-1,4-dione (**5**) and 23 mg (4%) of (3*S*)-1-acetyl-3-(3-indolylmethyl)-2,5-piperazinedione (**6**).

*Data for **4a***: ^{1}H-NMR ($CDCl_3$) δ: 7.11 (m, 2H, H-8, 10); 6.78 (t, *J*=7.4, H-9); 6.61 (d, *J*=7.7, H-7); 6.16 (br. s, 1H, NH^i); 5.78 (d, 1H, *J*=6.8, H-5a); 5.06 (br. s, 1H, N^2-H); 4.06 (m, 3H, H-3, H-10b, H-11a); 3.88 (dd, 1H, *J*=16.8 and 4.1, H-3); 2.72 (dd, 1H, *J*=13.1 and 6.1, H-11); 2.44 (m, 1H, H-11) ppm.

*Data for **1a***: Mp, 100–102°C. IR (KBr): 3265.2 (NH), 1678.3 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.02 (d, 1H, *J*=7.7, H-7); 7.28 (m, 2H, H-9, 10); 7.13 (t, 1H, *J*=7.1, H-8); 6.77 (br. s, 1H, NH); 6.42 (d, 1H, *J*=6.5, H-5a); 4.15 (t, 1H, *J*=6.7, H-10b); 4.08 (d, 1H, *J*=16.8, H-3); 3.88 (m, 2H, H-3, 11a); 2.73 (dd, 1H, *J*=12.7 and 5.5, H-11); 2.64 (s, 3H, Ac), 2.33 (m, 1H, H-11) ppm. $[\alpha]_D^{25}=-168.3$ (c 0.52, $CHCl_3$). Anal. calcd for $C_{15}H_{15}N_3O_3$: C, 63.16; H, 5.26; N, 14.74. Found: C, 62.76; H, 5.19; N, 14.32.

*Data for **5***: Mp, 78–80°C. IR (KBr): 3341.4 (NH), 1711.0 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.02 (d, 1H, *J*=7.7); 7.30 (m, 2H); 7.15 (t, 1H, *J*=7.2); 6.30 (d, 1H, *J*=5.9); 4.83 (d, 1H, *J*=17.1); 4.13 (m, 2H); 3.94 (d, 1H, *J*=17.1); 2.80 (dd, 1H, *J*=13.0 and 6.1); 2.64 (s, 3H); 2.55 (s, 3H); 2.45 (m, 1H) ppm. $[\alpha]_D^{25}=-116.0$ (c 0.28, $CHCl_3$). Anal. calcd for $C_{17}H_{17}N_3O_4$: C, 62.38; H, 5.20; N, 12.84. Found: C, 62.04; H, 5.45; N, 12.48.

*Data for **6***: Mp, 88–90°C. IR (KBr): 3321.3 (NH); 1699.0 (CO–NH). ^{1}H-NMR (d_6-DMSO) δ: 8.25 (br. s, 1H, NH^i); 7.56 (d, 1H, *J*=7.8, H-4′); 7.38 (d, 1H, *J*=8.0, H-7′); 7.16 (m, 2H, H-5′, 6′); 7.07 (d, 1H, *J*=2.1 Hz, H-2′); 6.24 (s, 1H, NH); 4.41 (m, 1H, H-3); 4.15 (d, 1H, *J*=18.1, H-6); 3.53 (d, 1H, *J*=18.1, H-6); 3.37 (m, 2H, Hβ-Trp); 2.55 (s, 3H, $COCH_3$) ppm. ^{13}C-NMR (d_6-DMSO) δ: 171.82 (*C*OCH_3); 168.79 and 166.27 (2CO); 136.37 (C-7′a); 126.61 (C-3′a); 124.21 (C-2′); 123.03 (C-4′); 120.31 (C-5′); 118.38 (C-6′); 111.70 (C-7′); 108.51 (C-3′); 57.10 (C-3); 45.81 (C-6); 30.31 (Cβ-Trp); 27.36 (CO*C*H_3) ppm. $[\alpha]_D^{25}=+15.7$ (c 0.14, DMSO). Anal. calcd for $C_{15}H_{15}N_3O_3$: C, 63.16; H, 5.26; N, 14.74. Found: C, 62.78; H, 5.67; N, 14.12.

*3.6. (3S,5aR,10bS,11aS)-6-Acetyl-3-isopropyl-1,3,4,5a,6,10b,11,11a-octahydro-2H-pyrazino[2′,1′-5,1]pyrrolo[2,3-b]indole-1,4-dione (**1b**)*

The method described for the synthesis of **1a** was used, starting from 560 mg (1.96 mmol) of compound **3b**. The yields obtained were: 291.2 (52%) of diketopiperazine **3b** and 177 mg (30%) of compound **1b**.

*Data for **4b***: 7.10 (m, 2H); 6.76 (t, 1H, *J*=7.4); 6.59 (d, 1H, *J*=7.7); 5.75 (d, 1H, *J*=6.9); 3.92 (m, 3H); 2.60 (m, 2H); 2.36 (m, 1H); 0.90 (d, 6H) ppm.

*Data for **1b***: Mp, 96–98°C. IR (KBr): 3285.7 (NH), 1741.5 and 1671.8 (2C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.04 (d, 1H, *J*=7.9); 7.35 (m, 2H); 7.12 (td, 1H, *J*=7.4 and 1.0); 6.48 (d, 1H, *J*=6.7); 6.25 (br. s, 1H); 4.15 (t, 1H, 6.8); 3.97 (br. s, 1H); 3.90 (dd, 1H, *J*=11.8 and 5.3); 2.69 (dd, 1H, *J*=12.6 and 5.3); 2.63 (s, 3H); 2.59 (m, 1H); 2.25 (m, 1H); 1.05 (d, 3H, *J*=7.2); 0.91 (d, 3H, *J*=6.8) ppm. ^{13}C-NMR ($CDCl_3$) δ: 170.90, 168.54, 165.12, 143.23, 130.49, 128.87, 124.99, 123.96, 118.46, 76.64, 60.52, 57.23, 43.74, 36.33, 29.32, 24.13, 19.07, 16.14 ppm. $[\alpha]_D^{25}=-108.2$ (c 0.50, $CHCl_3$). Anal. calcd for $C_{18}H_{21}N_3O_3$: C, 66.06; H, 6.42; N, 12.84. Found: C, 66.48; H, 6.78; N, 12.45.

3.7. Iminoethers derived from compounds **1**. General procedure

To a solution of the starting diketopiperazine (0.32 to 1.00 mmol) and triethyloxonium tetrafluoroborate (3 equiv.) in dry dichloromethane (50 ml) was added solid sodium carbonate (5 equiv.). The suspension was stirred at room temperature for 24–43 h, under an argon atmosphere, and was then poured onto ice water (3 ml). The organic layer was decanted from the aqueous phase, which was extracted with dichloromethane (5×10 ml). The combined organic layers were dried over sodium sulfate and evaporated. The residue was chromatographed on silica gel, eluting with petroleum ether:ethyl acetate (2:1). The yields obtained were: compound **7**, 40%; compound **9**, 60%; compound **13**, 61%; compound **14**, 71%; compound **16**, 68%; compound **19**, 17%.

*Data for **7***: Mp, 236–238°C. IR (KBr): 1703.5 and 1659.0 (2C=O, C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.11 (d, 1H, *J*=7.9, H-7); 7.25 (m, 2H, H-9, 10); 7.12 (t, 1H, *J*=7.4, H-8); 6.60 (d, 1H, *J*=7.1, H-5a); 4.12 (m, 5H, H-3, H-10b, OCH_2CH_3); 3.86 (m, 1H, H-11a); 2.60 (s, 3H, Ac); 2.55 (dd, 1H, *J*=12.3 and 5.2, H-11); 2.14 (m, 1H, H-11); 1.25 (t, 3H, *J*=7.2, OCH_2CH_3) ppm. ^{13}C-NMR ($CDCl_3$) δ: 171.06, 166.28, 159.33, 143.43, 130.48, 128.81, 124.75, 124.04, 119.07, 75.75, 61.87, 55.33, 51.83, 43.47, 37.95, 24.23, 14.25 ppm. $[\alpha]_D^{25}=-294.4$ (c 0.16, $CHCl_3$). Anal. calcd for $C_{17}H_{19}N_3O_3$: C, 65.18; H, 6.07; N, 13.42. Found: C, 64.82; H, 6.11; N, 13.11.

*Data for **9***: Mp, 188–189°C. IR (KBr): 3388.1 (NH); 1666.8 (2C=O, C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.10 (d, 1H, *J*=8.1); 7.24 (m, 2H); 7.12 (t, 1H, *J*=7.4); 6.54 (d, 1H, *J*=6.8); 4.11 (m, 4H); 3.89 (m, 1H); 2.63 (s, 3H); 2.56 (dd, 1H, *J*=12.4 and 4.9); 2.13 (m, 1H); 1.49 (d, 3H, *J*=7.1); 1.24 (t, 3H, *J*=7.1) ppm. $[\alpha]_D^{25}=-256.0$ (c 0.50, $CHCl_3$). Anal. calcd for $C_{18}H_{21}N_3O_3$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.89; H, 6.37; N, 12.60.

*Data for **13***: Mp, 225–226°C. IR (KBr): 1699.7 and 1661.1 (2C=O, C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.09 (d, 1H, *J*=7.9); 7.26 (m, 2H); 7.08 (m, 1H); 6.59 (d, 1H, *J*=7.2); 4.09 (m, 4H); 3.82 (dd, 1H, *J*=11.4 and 4.8); 2.55 (s, 3H); 2.53 (m, 1H); 2.08 (m, 1H); 1.34 (d, 3H, *J*=7.2); 1.21 (t, 3H, *J*=7.1) ppm. $[\alpha]_D^{25}=-200.6$ (c 0.50, $CHCl_3$). Anal. calcd for $C_{18}H_{21}N_3O_3$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.85; H, 6.52; N, 12.64.

*Data for **14***: Mp, 224°C. IR (KBr): 1700.0 and 1661.7 (2C=O, C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.12 (d, 1H, *J*=8.0); 7.26 (m, 2H); 7.11 (t, 1H, *J*=7.4); 6.63 (d, 1H, *J*=7.2); 4.11 (m, 4H); 3.85 (dd, 1H, *J*=11.8 and 5.1); 2.58 (s, 3H); 2.54 (m, 1H); 2.11 (m, 1H); 1.37 (d, 3H, *J*=7.2); 1.24 (t, 3H, *J*=7.1) ppm. $[\alpha]_D^{25}=+193.8$ (c 0.50, $CHCl_3$). Anal. calcd for $C_{18}H_{21}N_3O_3$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.82; H, 6.67; N, 12.62.

*Data for **16***: Mp, 187–188°C. IR (KBr): 1699.1 and 1662.2 (2C=O, C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.07 (d, 1H, *J*=7.9); 7.28 (m, 2H); 7.09 (t, 1H, *J*=7.4); 6.51 (d, 1H, *J*=6.9); 4.07 (m, 4H); 3.85 (m, 1H); 2.60 (s, 3H); 2.55 (dd, 1H, *J*=12.4 and 5.2); 2.13 (m, 1H); 1.47 (d, 3H, *J*=7.2); 1.22 (t, 3H, *J*=7.1) ppm. $[\alpha]_D^{25}=+251.8$ (c 0.50, $CHCl_3$). Anal. calcd for $C_{18}H_{21}N_3O_3$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.86; H, 6.71; N, 12.58.

*Data for **19***: Mp, 98–100°C. IR (KBr): 1671.6 (2C=O, C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.12 (d, 1H, *J*=8.0); 7.24 (m, 2H); 7.10 (td, 1H, *J*=7.4 and 1.1); 6.63 (d, 1H, *J*=7.2); 4.12 (m, 3H); 3.94 (t, 1H *J*=3.1); 3.82 (m, 1H); 2.64 (m, 1H); 2.60 (s, 3H); 2.50 (dd, 1H, *J*=12.1 and 5.0); 2.04 (m, 1H); 1.25 (t, 3H, *J*=7.1); 1.11 (d, 3H, *J*=6.9); 0.72 (d, 1H, *J*=6.8) ppm. $[\alpha]_D^{25}=-178.9$ (c 0.28, $CHCl_3$). Anal. calcd for $C_{20}H_{25}N_3O_3$: C, 67.61; H, 7.04; N, 11.83. Found: C, 67.97; H, 7.30; N, 11.44.

3.8. 10-Acetyl-5,7,8,9a,10,14b,15,15a-octahydroindolo[3′′,2′′-4′,5′]pyrrolo[2′,1′-3,4]-pyrazino[2,1-b]quinazoline-5,8-diones. General procedure

A mixture of the suitable iminoether (0.140 to 0.398 mmol) and anthranilic acid (2 equiv.) was melted at 140°C under a stream of argon and kept at this temperature for 4–6 h. The melt was cooled and triturated with 20% aqueous ammonium hydroxide, and the mixture was extracted with dichloromethane (5×5 ml). The combined organic layers were dried over sodium sulfate and evaporated. The residue was chromatographed on silica gel, eluting with petroleum ether:ethyl acetate (2:1). The yields obtained were: starting from iminoether **7**, 76% of compound **8**; starting from iminoether **9**, 23% of compound **10**, 8% of compound **11**[15] and 3% of compound **12**; starting from iminoether **13**, 44% of compound **12**; starting from iminoether **14**, 38% of compound **15**; starting from iminoether **16**, 20% of compound **17**, 13% of compound **18** and 4% of compound **15**; starting from iminoether **19**, 14% of compound **20** and 45% of compound **21**.

*Data for **8***: Mp, 285–287°C. IR (KBr): 1678.9 (2C=O, C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.26 (dd, 1H, *J*=8.0 and 1.2, H-4); 8.04 (d, 1H, *J*=7.7, H-11); 7.78 (td, 1H, *J*=8.3 and 1.5, H-2); 7.66 (d, 1H, *J*=7.6, H-1); 7.50 (t, *J*=8.0, H-3); 7.34 (m, 2H, H-12, 14); 7.27 (t, 1H, *J*=7.0, H-13); 6.37 (d, 1H, *J*=6.1, H-9a); 5.24 (d, 1H, *J*=17.6, H-7); 4.54 (dd, 1H, *J*=10.8 and 5.7, H-15a); 4.26 (t, 1H, *J*=6.3, H-14b); 4.20 (d, 1H, *J*=17.6, H-7); 3.12 (dd, 1H, *J*=13.1 and 5.8, H-15); 2.71 (m, 1H, H-15); 2.68 (s, 3H, Ac) ppm. $[\alpha]_D^{25}$=+10.2 (c 0.22, $CHCl_3$). Anal. calcd for $C_{22}H_{18}N_4O_3$: C, 68.39; H, 4.66; N, 14.51. Found: C, 68.08; H, 4.35; N, 14.47.

*Data for **10***: Mp, 187–188°C. IR (KBr): 1676.1 (2C=O, C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.25 (dd, 1H, *J*=8.0 and 1.0); 8.21 (d, 1H, *J*=8.1); 7.75 (t, 1H, *J*=7.6); 7.51 (m, 2H); 7.29 (m, 2H); 7.16 (t, 1H, *J*=7.2); 6.86 (d, 1H, *J*=7.8); 5.42 (q, 1H, *J*=7.0); 4.54 (dd, 1H, *J*=12.5 and 4.8); 4.29 (t, 1H, *J*=7.9); 2.76 (dd, 1H, *J*=10.0 and 4.9); 2.50 (s, 3H); 2.32 (m, 1H); 1.70 (d, 3H, *J*=7.0) ppm. ^{13}C-NMR ($CDCl_3$) δ: 170.82, 167.96, 160.20, 147.79, 146.99, 143.91, 135.16, 129.47, 129.23, 127.45, 127.00, 126.79, 124.87, (double signal), 120.51, 117.15, 76.79, 58.23, 52.23, 44.53, 41.83, 24.43, 21.11 ppm. $[\alpha]_D^{25}$=−34.0 (c 0.50, $CHCl_3$). Anal. calcd for $C_{23}H_{20}N_4O_3$: C, 68.99; H, 5.03; N, 13.99. Found: C, 69.02; H, 5.20; N, 13.77.

*Data for **11***: Mp, 135°C. IR (KBr): 1680.1 (2C=O, C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.15 (dd, 1H, *J*=8.0 and 1.2); 7.77 (d, 1H, *J*=8.0); 7.71 (dd, 1H, *J*=6.9 and 1.4); 7.60 (d, 1H, *J*=7.6); 7.42 (t, 1H, *J*=7.5); 7.26 (t, 1H, *J*=7.7); 7.06 (t, 1H, *J*=7.7); 6.91 (t, 1H, *J*=7.5); 6.23 (d, 1H, *J*=6.0); 5.37 (q, 1H, *J*=7.3); 4.90 (dd, 1H, *J*=10.0 and 3.4); 4.11 (m, 1H); 3.72 (dd, 1H, *J*=11.5 and 5.9); 2.89 (m, 1H); 2.60 (s, 3H); 1.60 (d, 3H, *J*=7.4) ppm. $[\alpha]_D^{25}$=+101.0 (c 0.80, $CHCl_3$). Anal. calcd for $C_{23}H_{20}N_4O_3$: C, 68.99; H, 5.03; N, 13.99. Found: C, 68.77; H, 5.27; N, 13.98.

*Data for **12***: Mp, 262–263°C. IR (KBr): 1681.9 (2C=O, C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.27 (d, 1H, *J*=7.3); 8.06 (d, 1H, *J*=7.7); 7.77 (td, 1H, *J*=8.4 and 1.5); 7.65 (d, 1H, *J*=8.2); 7.50 (t, 1H, *J*=7.0); 7.36 (m, 2H); 7.18 (t, 1H, *J*=7.4); 6.37 (d, 1H, *J*=6.1); 5.44 (q, 1H, *J*=7.1); 4.55 (dd, 1H, *J*=10.8 and 5.7); 4.25 (t, 1H, *J*=6.3); 3.17 (dd, 1H, *J*=13.1 and 5.7); 2.71 (s, 3H); 2.67 (m, 1H); 1.50 (d, 3H, *J*=7.1) ppm. $[\alpha]_D^{25}$=−49.8 (c 0.41, $CHCl_3$). Anal. calcd for $C_{23}H_{20}N_4O_3$: C, 68.99; H, 5.03; N, 13.99. Found: C, 68.80; H, 5.28; N, 13.69.

*Data for **15***: Mp, 263–264°C. IR (KBr): 1680.4 (2C=O, C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.25 (d, 1H, *J*=7.3); 8.05 (d, 1H, *J*=7.6); 7.77 (td, 1H, *J*=8.3 and 1.4); 7.65 (d, 1H, *J*=8.1); 7.50 (t, 1H, *J*=6.9); 7.36 (m, 2H); 7.17 (t, 1H, *J*=7.4); 6.37 (d, 1H, *J*=6.1); 5.44 (q, 1H, *J*=7.0); 4.54 (dd, 1H, *J*=10.7 and 5.6); 4.25 (t, 1H, *J*=6.3); 3.17 (dd, 1H, *J*=13.0 and 5.7); 2.71 (s, 3H); 2.67 (m, 1H); 1.50 (d, 3H, *J*=7.1) ppm. $[\alpha]_D^{25}$=+49.2 (c 0.25, $CHCl_3$). Anal. calcd for $C_{23}H_{20}N_4O_3$: C, 68.99; H, 5.03; N, 13.99. Found: C, 68.74; H, 5.00; N, 13.69.

*Data for **17***: Mp, 185–186°C. IR (KBr): 1679.7 (2C=O, C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.28 (d,

1H, *J*=7.9); 8.22 (d, 1H, *J*=8.2); 7.77 (td, 1H, *J*=7.7 and 1.5); 7.52 (m, 2H); 7.30 (m, 2H); 7.16 (t, 1H, *J*=7.3); 6.87 (d, 1H, *J*=7.8); 5.43 (q, 1H, *J*=7.0); 4.55 (dd, 1H, *J*=12.5 and 4.8); 4.30 (t, 1H, *J*=7.9); 2.77 (dd, 1H, *J*=12.0 and 4.9); 2.50 (s, 3H); 2.34 (m, 1H); 1.71 (d, 3H, *J*=7.0) ppm. $[\alpha]_D^{25}$=+50.3 (c 0.17, $CHCl_3$). Anal. calcd for $C_{23}H_{20}N_4O_3$: C, 68.99; H, 5.03; N, 13.99. Found: C, 68.86; H, 5.20; N, 13.69.

Data for ***18***: Mp, 135–136°C. IR (KBr): 1679.8 (2C=O, C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.15 (dd, 1H, *J*=7.9 and 1.1); 7.77 (d, 1H, *J*=8.0); 7.71 (dd, 1H, *J*=6.9 and 1.3); 7.61 (d, 1H, *J*=7.6); 7.43 (t, 1H, *J*=7.4); 7.26 (t, 1H, *J*=7.7); 7.06 (t, 1H, *J*=7.6); 6.90 (t, 1H, *J*=7.5); 6.23 (d, 1H, *J*=5.9); 5.37 (q, 1H, *J*=7.2); 4.91 (dd, 1H, *J*=10.0 and 3.3); 4.11 (m, 1H); 3.72 (dd, 1H, *J*=11.4 and 5.9); 2.88 (m, 1H); 2.60 (s, 3H); 1.59 (d, 3H, *J*=7.4) ppm. $[\alpha]_D^{25}$=−110.7 (c 1.14, $CHCl_3$).

Data for ***20***: Mp, 77–80°C. IR (KBr): 1677.8 (2C=O, C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.25 (d, 1H, *J*=6.5); 8.17 (d, 1H, *J*=8.0); 7.90 (d, 1H, *J*=8.4); 7.76 (m, 2H); 7.53 (m, 2H); 7.18 (m, 1H); 6.11 (d, 1H, 7.7); 5.36 (d, 1H, *J*=3.1); 4.60 (dd, 1H, *J*=12.0 and 5.2); 4.28 (t, 1H, *J*=6.5); 2.83 (dd, 1H, *J*=14.1 and 5.6); 2.60 (s, 3H); 2.50 (m, 1H); 2.05 (m, 1H); 1.32 (d, 3H, *J*=6.9); 0.92 (d, 3H, *J*=6.9) ppm. $[\alpha]_D^{25}$=+23.1 (c 0.07, $CHCl_3$). Anal. calcd for $C_{25}H_{23}N_4O_3$: C, 70.26; H, 5.39; N, 13.11. Found: C, 69.85; H, 5.19; N, 12.90.

Data for ***21***: Mp, 92–94°C. IR (KBr): 1678.6 (2C=O, C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.14 (dd, 1H, *J*=8.0 and 1.2); 7.71 (m, 2H); 7.59 (d, 1H, *J*=7.4); 7.42 (td, 1H, *J*=8.1 and 1.2); 7.25 (d, 1H, *J*=6.9); 7.00 (t, 1H, *J*=7.7); 6.80 (t, 1H, *J*=6.6); 6.22 (d, 1H, *J*=5.8); 5.15 (d, 1H, *J*=9.8); 4.95 (dd, 1H, *J*=9.8 and 2.6); 4.08 (t, 1H, *J*=6.7); 3.77 (br. d, 1H, *J*=15.4); 2.83 (m, 1H); 2.59 (s, 3H); 2.26 (m, 1H); 1.23 (d, 3H, *J*=6.7); 0.93 (d, 3H, *J*=6.7) ppm. $[\alpha]_D^{25}$=+121.6 (c 0.44, $CHCl_3$). Anal. calcd for $C_{25}H_{23}N_4O_3$: C, 70.26; H, 5.39; N, 13.11. Found: C, 70.56; H, 5.28; N, 12.89.

*3.9. (3S,5aR,10bS,11aS)-6-Acetyl-2-(o-azidobenzoyl)-3-methyl-1,3,4,5a,6,10b,11,11a-octahydro-2H-pyrazino[2′,1′-5,1]pyrrolo[2,3-b]indole-1,4-dione (**22**)*

o-Azidobenzoyl chloride was prepared by heating at 80°C for 3 h, under an argon atmosphere a solution of *o*-azidobenzoic acid (326 mg, 6.0 mmol) in thionyl chloride (2.18 ml, 90 mmol). The excess thionyl chloride was evaporated under reduced pressure. Dry benzene (2×5 ml) was added to the residue and evaporated. The crude *o*-azidobenzoyl chloride was inmediately used for the acylation step, which was performed as follows. To a cooled (−78°C) solution of compound **1c**[8] (100 mg, 0.33 mmol) in dry THF (20 ml) was dropwise added a 0.5 M solution of potassium hexamethyldisilazide in toluene (0.8 ml, 1.2 equiv.). The solution was stirred at −78°C for 15 min, becoming intensely yellow, and was then treated with a solution of the crude *o*-azidobenzoyl chloride in THF (10 ml). The solution was stirred at −78°C for 3 h, was left to warm to room temperature over 20 h and was then poured over saturated aqueous ammonium chloride (10 ml), which was extracted with dichloromethane (6×10 ml). The combined dichloromethane layers were dried over sodium sulfate and evaporated, and the residue was chromatographed on silica gel, eluting with petroleum ether:ethyl acetate (4:1). Yield, 79.1 mg (54%) of compound **22**. Mp, 74–75°C. IR (KBr): 2129.6 (N_3); 1680.2 (2C=O, C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.18 (d, 1H, *J*=8.3, H-7); 7.46 (td, 1H, *J*=7.8 and 1.6, H-5′); 7.37 (dd, 1H, *J*=7.7 and 1.5, H-6′); 7.28 (m, 2H, H-9, 10); 7.20 (m, 1H, H-3′); 7.12 (m, 2H, H-4′, 8); 6.73 (d, 1H, *J*=7.5, H-5a); 5.06 (q, 1H, *J*=7.0, H-3); 4.22 (t, 1H, *J*=7.5, H-10b); 4.13 (dd, 1H *J*=12.4 and 5.0, H-11a); 2.57 (s, 3H, Ac); 2.53 (dd, *J*=12.2 and 5.0, H-11); 2.23 (m, 1H, H-11); 1.68 (d, 3H, *J*=7.8, C_3–CH_3) ppm. $[\alpha]_D^{25}$=−63.3 (c 0.62, $CHCl_3$). Anal. calcd for $C_{23}H_{20}N_6O_4$: C, 62.16; H, 4.50; N, 18.92. Found: C, 61.97; H, 4.69; N, 18.63.

*3.10. Alternative synthesis of compound **10** by intramolecular aza Wittig reaction of compound **22***

To a solution of compound **22** (36.8 mg, 0.083 mmol) in dry toluene (5 ml) was added tributylphosphine (30 μl, 0.13 mmol). The solution was stirred at room temperature for 2 h. The solvent was evaporated and the residue was chromatographed on silica gel, eluting with petroleum ether:dichloromethane (2:1) and then with ethyl acetate. Yield, 27 mg (81%) of compound **10**, as a white solid.

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14. This behavior is similar to the one found by Rajappa and Advani for a similar reaction of *cyclo*-(L-Pro–L-Val), although they do not give the actual yields of both stereoisomers. See Ref 6a.
15. Compounds **11** and **15** were initially recovered as a mixture with compounds **1c** and **1f**, respectively, arising from the hydrolysis of the starting iminoethers. Their chromatographic separation was not possible, and therefore the mixture was treated with triethyloxonium tetrafluoroborate to transform **1c** and **1f** into **9** and **14**, respectively, which allowed the purification of the hexacyclic compounds **11** and **15**.