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TETRAHEDRON: *ASYMMETRY*

Stereochemical issues related to the synthesis of 7,10-dimethyl-7,10,16,16a-tetrahydro-11*H*-quinazolino[2′,3′:3,4]pyrazino-[1,2-*b*]β-carboline-5,8-diones

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Abstract

Condensation reactions between anthranilic acid and iminoethers derived from 2,3,6,7,12,12a-hexahydropyrazino[1,2-*b*]β-carboline-1,4-diones **3**–**8** to give the title hexacyclic compounds were studied from a stereochemical point of view. The configuration was retained in the formation of iminoethers, but inversion of the tryptophan sterocenter C-16a took place in the condensation process. Epimerization also occurred in an alternative procedure that involves acylation at N-2 with *o*-azidobenzoyl chloride, followed by intramolecular aza-Wittig reaction.

1. Introduction

Our current interest in multi drug resistance (MDR) reversal agents, designed as analogs of the fungal metabolite *N*-acetylardeemin (**1**),[1,2] moved us to study the dehydro-*C*-homo analogs **2**, in which rings A–C have been modified to a 1,2,3,4-tetrahydro-β-carboline system. These compounds could be potentially used in combination with antitumor drugs to avoid resistances related to the overexpression of the membrane glycoprotein P-170, that lowers the intracellular concentrations of several antitumor agents below their therapeutic levels.[3] Their synthesis was planned through condensation with anthranilic acid of the tetracyclic piperazinediones containing the A–D fragment, with special concern given to the possible epimerization of stereogenic centers, especially of C-16a (Scheme 1).

Condensation with anthranilic acid of iminoethers with one or two stereocenters derived from proline dipeptide anhydrides may affect the proline stereocenter. Thus, epimerization took place in the reactions of anthranilic acid with iminoethers derived from *cyclo*-L-Pro-Gly and *cyclo*-L-Val-L-Pro, but not in those of *cyclo*-D-Val-L-Pro and *cyclo*-Sar-L-Ala.[4]

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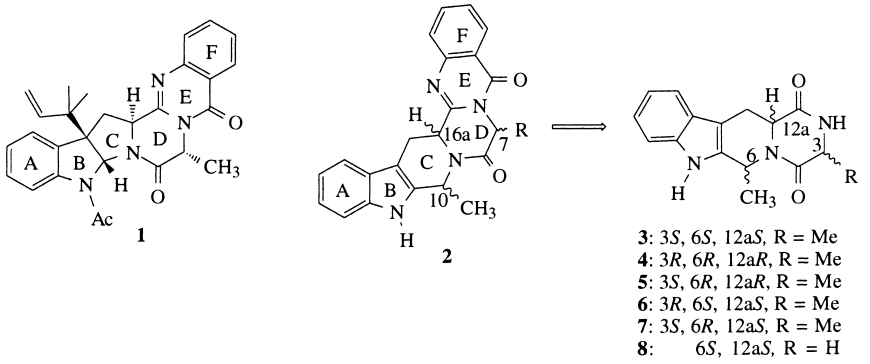
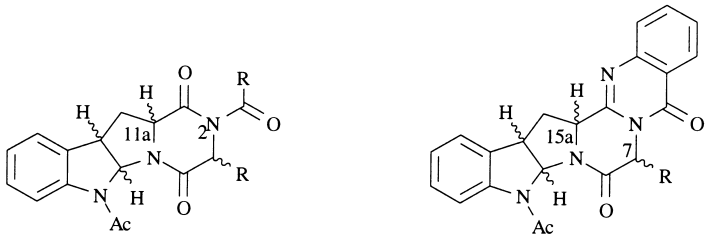


Scheme 1.

We have recently studied the fate of the tryptophan stereocenter in the acylation at the N-2 position of 3,5a,6,10b,11,11a-hexahydro-2*H*-pyrazino[2′,1′-5,1]pyrrolo[2,3-*b*]indole-1,4-diones to give compounds **A**, which are precursors of *N*-acetylardeemin,[5a] and in the condensation of the corresponding iminoethers with anthranilic acid,[5b] to obtain analogs **B**.



A **B**

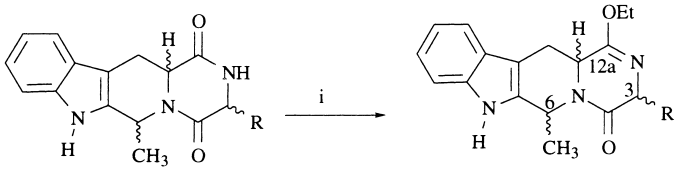
In the first case, we observed epimerization at C-11a in compounds with a *syn*-relationship between H-3 and H-11a hydrogen atoms. In the second case, the stereochemistry of all stereocenters was retained in compounds with an *anti*-relationship between H-7 and H-15a protons when R=H or R=Me, while partial epimerization at C-15a was observed for derivatives with R=Me and with a *syn*-relationship between H-7 and H-15a protons. These observations were explained taking into account the steric compression between the N-2 acyl, the C-1 oxygen and the C-3 methyl groups or between the C-7 methyl and the C-5 and C-8 carbonyl groups in the most probable conformation of ring D in the **A** or **B** systems.

2. Results and discussion

We study here the stereochemistry of these transformations in the tetracyclic piperazinediones **3**–**8** (Scheme 1), which were prepared from (1*S*,3*S*), (1*R*,3*R*) and (1*R*,3*S*) methyl 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylates through their reaction with glycine, or L or D-alanine, followed by cyclization of the dipeptides thus obtained to the corresponding cyclic anhydrides.[6]

Activation of the amide function in compounds **3**–**8** by transformation into the iminoethers **9**–**14**[7] was required to achieve the hexacyclic compounds in the subsequent reaction with anthranilic acid. The alternative procedure to obtain 4-quinazolones from amides by direct reaction with anthranilic acid and thionyl chloride, which has been exploited by Kametani and coworkers for the synthesis of natural products,[8] did not work in our case (Scheme 2).

This process took place with retention of the configuration of all stereocenters, according to ^{1}H-NMR



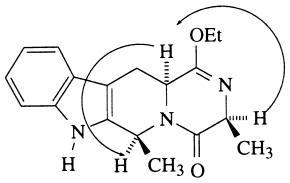
3-8 9-14

Compound	C-3	C-6	C-12a	(%) Yield
9	*S*	*S*	*S*	92
10	*R*	*R*	*R*	91
11	*S*	*R*	*R*	66
12	*R*	*S*	*S*	71
13	*S*	*R*	*S*	20
14		*S*	*S*	74

Reagents and conditions, i: $Et_3O^+ BF_4^-$, Na_2CO_3, CH_2Cl_2, r.t., 43h.

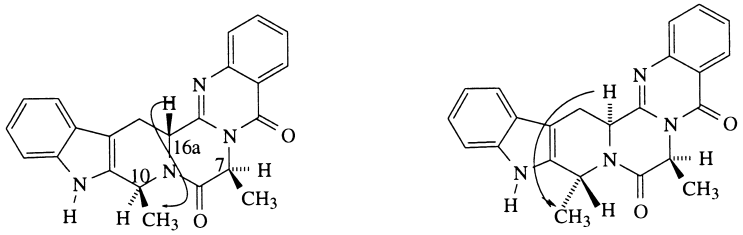
Scheme 2.

experiments. For instance, the *syn*-relationship between H-3, H-6 and H-12a protons in enantiomers **9** and **10** was confirmed by the NOE effects shown for compound **9** and by the homoallylic coupling (J=2.6 Hz) between H-3 and H-12a protons, which was confirmed by COSY experiments. This coupling was absent in compounds **11** and **12**.[9]



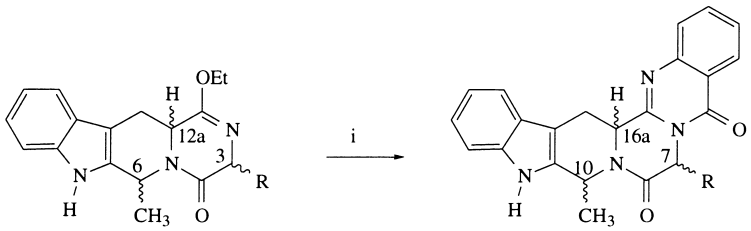
9

Treatment of iminoethers **9**–**14** with excess anthranilic acid gave the hexacycles **15**–**20** with inversion of the stereocenter C-16a during the cyclization (Scheme 3). This was confirmed in all compounds by NOE experiments (see for instance those of diagnostic value for compounds **15** and **16**). The high chemical shift value of the H-7 proton (δ H-7=5.28–5.46 ppm, Table 1) confirms that it is coplanar with the C-5 carbonyl group, as it occurs in simpler pyrazinoquinazolinediones containing the D–F fragment.[2,4] This means that ring D is anchored by the C-7 methyl substituent into a pseudoaxial configuration. On the other hand, the H-10 hydrogen atom is also nearly coplanar with the C-8 carbonyl group, being highly deshielded (δ H-10=6.02–6.07 ppm).



15 **16**

Due to the nearly planar chair conformation that can be assumed for ring C^{10} and the coplanarity of H-7 and H-10 with C_5=O and C_8=O groups, respectively, it could be argued that with the epimerization of the tryptophan stereocenter in compounds **15**, **16** and **19**, important steric interactions between the methyl group at C-7 and the C^{16a}–C^{16} bond were released (Fig. 1),[11] while the epimerization found



9-14 **15-20**

Comp.	R	C-7	C-10	C-16a	(%) Yield
15	CH_3	*S*	*S*	*R*	21
16	CH_3	*R*	*R*	*S*	20
17	CH_3	*S*	*R*	*S*	12
18	CH_3	*R*	*S*	*R*	12
19	CH_3	*S*	*R*	*R*	12
20	H		*S*	*R*	40

Reagents and conditions, i: Anthranilic acid (2 equiv.), 130 °C, 2h

Scheme 3.

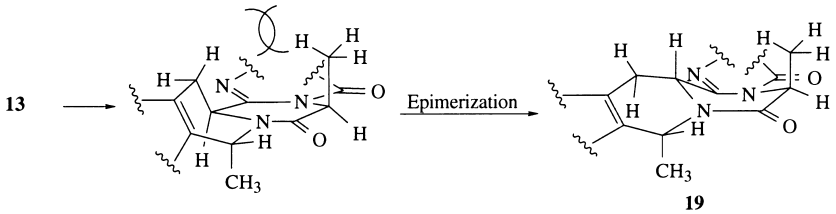


Fig. 1.

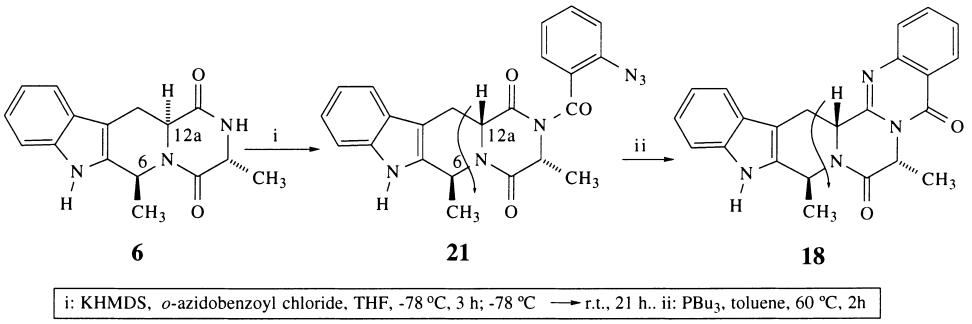
in the case of compounds **17**, **18** and **20** was not expected, a possible factor being the interaction between the methyl substituent at C-10 and the carbonyl group at C-8, which may be prevented. The enantiomeric relationships between compounds **3**–**4**, **5**–**6**, **9**–**10**, **11**–**12**, **15**–**16** and **17**–**18** were reflected in their experimental optical rotations.

To explore the stereochemistry of the alternative route to the hexacycles previously mentioned,[12,13] we assayed the reaction of piperazinedione **6** with *o*-azidobenzoyl chloride in the presence of KHMDS. These reaction conditions permitted the benzoylation at N-2 of pyrazino[2′,1′-5,1]pyrrolo[2,3-*b*]indole-1,4-diones with retention of stereochemistry, even in compounds with a *syn*-relationship between the two CH protons of the piperazinedione ring.[1c,5a,b] However compound **6** gave as the only reaction product the *ortho*-azidobenzoyl derivative **21**, with epimerization of the tryptophan sterocenter according to NOE experiments. As expected, treatment of this intermediate with tributylphosphine afforded hexacycle **18** through an intramolecular aza-Wittig coupling (Scheme 4).

To rationalize the stereochemistry of compound **21**, we can assume that the steric compression between the N^2–acyl, the C^1=O and the C^3–methyl groups is relieved by epimerization of C12a.

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 a fluorescent indicator (Macherey-Nagel Alugram Sil



Scheme 4.

G/UV_{254}). Separations by flash chromatography were performed on silica gel (SDS 60 ACC, 230–400 mesh). Catalytic hydrogenations were carried out using a Parr 3920 shaking reactor. Melting points were measured on a Reichert 723 hot stage microscope, and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Paragon 1000 FT-IR spectrophotometer, with solid compounds compressed into KBr pellets and liquid compounds placed (neat or dissolved in the minimum amount of bromoform) between NaCl plates. NMR spectra were obtained on a Bruker AC-250 spectrometer (250 MHz for ^{1}H, 63 MHz for ^{13}C) spectrometer (Servicio de Espectroscopía, Universidad Complutense), with $CDCl_3$ or DMSO-d_6 as solvents. When necessary, assignments were aided by DEPT, COSY and ^{13}C–^{1}H 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. Combustion elemental analyses were determined by the Servicio de Microanálisis, Universidad Complutense, on a Perkin–Elmer 2400 CHN microanalyzer.

3.1. *Synthesis of piperazinedione* ***8***

N-Boc-Glycine (3.68 mmol) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) (5.44 mmol) were added to methyl (1*S*,3*S*) 1-methyl-β-carboline-3-carboxylate[6] (3.68 mmol). The reaction was protected with an anhydrous calcium chloride tube and was magnetically stirred in the dark for 24 h. After concentration to dryness at low pressure, the residue was extracted with a mixture of chloroform (15 ml) and 1 N hydrochloric acid (16 ml). The separated organic phase was washed with 1 N sodium bicarbonate (15 ml), dried and concentrated. Purification of the residue by column chromatography with chloroform gave methyl (1*S*,3*S*) 1,2,3,4-tetrahydro-1-methyl-2-*tert*-butoxyglycyl-β-carboline-3-carboxylate, 1.05 g (71%) as a white solid. Mp 109–110°C. IR (KBr): 3330, 1740, 1692 and 1655 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.14 (br. s, 1H); 7.49 (d, 1H, *J*=7.3 Hz); 7.30 (d, 1H, *J*=8.1 Hz); 7.15 (m, 2H); 5.72 (s, 1H); 5.57 (q, 1H, *J*=6.5 Hz); 4.13 (d, 1H, *J*=5.9 Hz); 4.10 (m, 2H); 3.62 (s, 3H); 3.50 (m,1H); 1.49 (m, 6H); 1.45 (s, 9H) ppm. ^{13}C-NMR ($CDCl_3$) δ: 171.8; 170.9; 168.6; 156.2; 136.4; 133.0; 126.5; 122.3; 119.8; 118.5; 111.0; 104.7; 52.9; 49.9; 47.8; 43.3; 42.9; 28.5; 19.5 ppm. Anal. calcd for $C_{21}H_{27}N_3O_5$: C, 62.83; H, 6,78; N, 10.47. Found: C, 62.90; H, 6.85; N, 10.25.

Heating the above dipeptide (1.2 g, 3.12 mmol) at 200°C for 2 h, under a stream of argon, followed by purification by column chromatography on silica gel (ethyl acetate:chloroform=1:2), afforded 0.8 g (90.4% yield) of compound **8**. Mp 228–229°C. IR (KBr): 3334; 1720 and 1656 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 11.03 (s, 1H); 8.31 (s, 1H); 7.5 (d, 1H; *J*=7.1 Hz); 7.27 (d, 1H; *J*=7.5 Hz); 7.01 (m, 2H); 5.23 (q, 1H, *J*=5.9 Hz); 4.17 (d, 1H, *J*=9.5 Hz); 3.8 (dd, 2H, J=64.4 and 17.02 Hz); 2.74 (dd, 1H, *J*=14.6 and 12.8 Hz); 1.37 (d, 3H, *J*=5.9 Hz) ppm. ^{13}C-NMR (DMSO-d_6) δ: 170.4; 169.4; 137.6; 137.4; 127.7; 122.7;

120.5; 113; 119.6; 106.3; 56.7; 49.5; 46.5; 25.1; 23.9 ppm. $[\alpha]_D^{25}$=+382 (*c* 0.1, EtOH). Anal. calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.91; H, 5.66; N, 15.75.

*3.2. Activation of piperazinediones. General method. Synthesis of iminoethers **9–14***

To a solution of the starting piperazinedione (0.35 mmol) and triethyloxonium tetrafluoroborate (3 equiv.) in dry dichloromethane (50 ml), was added anhydrous sodium carbonate (5 equiv.). The suspension was stirred at room temperature under a stream of argon for 16 h, and was then poured onto ice water. The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure. The residue was used in the next reaction without further purification.

Data for **9** and **10**: ^{1}H-NMR ($CDCl_3$) δ: 8.97 (s, 1H); 7.56 (d, 1H, *J*=7.1 Hz); 7.37 (d, 1H, *J*=7.0 Hz); 7.15 (m, 2H); 5.44 (q, 1H, *J*=6.0 Hz); 4.16 (m, 3H); 3.92 (m, 1H); 3.50 (dd, 1H, *J*=15.5 and 4.0 Hz); 2.94 (dd, 1H, *J*=15.5 and 11.8 Hz); 1.62 (d, 3H, *J*=6.0 Hz); 1.50 (d, 3H, *J*=7.1 Hz); 1.37 (t, 3H, *J*=6.8 Hz) ppm. ^{13}C-NMR δ: 173.4; 160.9; 136.0; 135.7; 126.1; 121.7; 119.6; 117.9; 111.3; 62.1; 55.4; 54.3; 48.6; 23.3; 23.0; 14.1 ppm.

Data for **11** and **12**: ^{1}H-NMR ($CDCl_3$) δ: 9.04 (s, 1H); 7.50 (d, 1H, *J*=6.9 Hz); 7.37 (d, 1H, *J*=7.1 Hz); 7.17 (m, 2H); 5.42 (q, 1H, *J*=6.5 Hz); 4.19 (m, 3H); 3.94 (m, 1H); 3.57 (dd, 1H, *J*=15.2 and 4.2 Hz); 3.10 (dd, 1H, *J*=15.2 and 11.8 Hz); 1.68 (d, 3H, *J*=6.2 Hz); 1.58 (d, 3H, *J*=6,5 Hz); 1.25 (t, 3H, *J*=7.0 Hz) ppm.

Data for **13**: ^{1}H-NMR ($CDCl_3$) δ: 9.24 (s, 1H); 7.57 (d, 1H, *J*=7.0 Hz); 7.37 (d, 1H, *J*=6.9 Hz); 7.08 (m, 2H); 5.40 (q, 1H, *J*=6.1 Hz); 4.22 (m, 3H); 3.90 (m, 1H); 3.50 (dd, 1H, *J*=15.4 and 3.7 Hz); 2.90 (dd, 1H, *J*=15.4 and 12.0 Hz); 1.62 (d, 3H, *J*=6.1 Hz); 1.38 (d, 3H, *J*=6.8 Hz); 1.22 (t, 3H, *J*=7.1 Hz) ppm.

Data for **14**: ^{1}H-NMR ($CDCl_3$) δ: 9.42 (s, 1H); 7.55 (d, 1H, J=7.2 Hz); 7.38 (d, 1H, *J*=6.9 Hz); 7.12 (m, 2H); 5.44 (q, 1H, *J*=6.2 Hz); 4.02 (m, 1H); 3.90 (m, 1H); 3.48 (dd, 1H, *J*=14.7 and 4.1 Hz); 2.95 (dd, 1H, *J*=14.7 and 11.6 Hz); 1.67 (d, 3H, *J*=4.4 Hz); 1.50 (d, 3H, *J*=6.2 Hz); 1.38 (t, 3H, *J*=7.1 Hz) ppm.

*3.3. Synthesis of 7,10,16,16a-tetrahydroquinazolino[2′,3′:3,4]pyrazino[1,2-*b*]β-carboline-5,8-diones. General method*

A mixture of the corresponding iminoether (0.22 mmol) and anthranilic acid (0.68 mmol) was melted at 130°C under a stream of argon for 2 h. The melt was cooled and triturated with 20% aqueous ammonium hydroxide (2 ml), and the mixture was extracted with chloroform. The combined organic layers were dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel, eluting with dichloromethane.

Data for **15**: Mp: 211–212°C. IR (KBr): 3308, 1688, 1634 and 1646. $[\alpha]_D^{25}$=+240 (*c* 0.8, EtOH). Anal. calcd for $C_{23}H_{20}N_4O_2$: C, 71.86; H, 5.24; N, 14.57. Found: C, 72.04; H, 5.08; N, 14.52.

Data for **16** were identical to those of compound **15**. $[\alpha]_D^{25}$=−232 (*c* 0.8, EtOH).

Data for **17**: Mp: 201–202°C. IR (KBr): 3290, 1667, 1622 and 1610. $[\alpha]_D^{25}$=+205 (*c* 0.2, EtOH). Anal. calcd for $C_{23}H_{20}N_4O_2$: C, 71.86; H, 5.24; N, 14.57. Found: C, 72.17; H, 5.07; N, 14.50.

Data for **18** were identical to those of compound **17**. $[\alpha]_D^{25}$=+186 (*c* 0.2, EtOH).

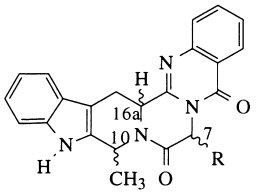
Data for **19**: Mp: 257–258°C. $[\alpha]_D^{25}$=+182.85 (*c* 0.07, $CHCl_3$). Anal. calcd for $C_{23}H_{20}N_4O_2$: C, 71.86; H, 5.24; N, 14.57. Found: C, 71.17; H, 5.07; N, 14.10.

Data for **20**: Mp: 266–267°C. $[\alpha]_D^{25}$=+407 (*c* 0.1, $CHCl_3$). Anal. calcd for $C_{22}H_{18}N_4O_2$: C, 71.34; H, 4.9; N, 15.13. Found: C, 71.38; H, 4.95 N; 15.05.

NMR data for compounds **15**–**20** are given in Tables 1 and 2.

Table 1
^{1}H-NMR data of compounds **15–20**

Compound	C-7	C-10	C-16a
15	*S*	*S*	*R*
16	*R*	*R*	*S*
17	*S*	*R*	*S*
18	*R*	*S*	*R*
19	*S*	*R*	*R*
20		*S*	*R*



15-19 ; R = CH_3
20; R= H

Signal	**15** and **16**	**17** and **18**	**19**	**20**
C_4-H	8.32 (d, *J*= 7.8 Hz)	8.34 (d, *J* = 7.8 Hz)	8.20 (d, *J*= 7.1 Hz)	8.30 (d, *J*= 8.0 Hz)
N_{11}-H	8.10 (s)	8.12 (s)	7.82 (s)	8.18 (s)
C_2-H	7.81 (m)	7.80 (m)	7.7 (t, *J* = 8.2 Hz)	7.80 (t, *J* = 6.9 Hz)
C_1-H	7.81 (m)	7.80 (m)	7.62 (d, *J* = 7.3 Hz)	7.72 (d, *J* = 7.4 Hz)
C_3 and C_{15}-H	7.52 (m)	7.7 (d, *J* = 7.6 Hz)	7.41 (t, *J* = 8 Hz)	7.52 (m)
C_{12}-H	7.37 (d, *J* =7.8 Hz)	7.38 (d, *J* = 7.8 Hz)	7.26 (d, *J* = 7.7 Hz)	7.37 (d, *J* = 7.9 Hz)
C_{13} and C_{14}-H	7.16 (m)	7.17 (m)	7.05 (m)	7.12 (m)
C_{10}-H	6.02 (q, *J* = 6.6 Hz)	6.07 (q, *J* = 7 Hz)	5.91 (q, *J* = 6.7 Hz)	6.02 (q, *J* = 8.2 Hz)
C_7-H	5.40 (q, J= 6.7 Hz)	5.46 (q, *J* = 7 Hz)	5.28 (q, *J* = 6.73 Hz)	5.44 (m) and 2.26 (m)
C_{16a}-H	5.0 (dd, *J* = 13.5 and 4.4 Hz)	5.06 (dd, *J* = 11.8 and 4.1 Hz)	4.90 (dd, *J* = 4.2 and 10.6 Hz)	4.98 (dd, *J* = 10.9 and 4.4 Hz)
C_{16}-H eq	3.80 (dd, *J* = 15.7 and 4.4 Hz)	3.60 (dd, *J* = 15 and 4.1 Hz)	3.78 (dd, *J* = 4.4 and 15.7 Hz)	3.82 (dd, *J* = 15.7 and 4.4 Hz)
C_{16}-H ax	2.96 (dd, *J* = 13.5 and 15.7 Hz)	3.12 (dd, *J* = 11.8 and 15 Hz)	2.88 (dd, *J* = 10.8 and 15.7 Hz)	2.86 (dd, *J* = 11.0 and 9.5 Hz)
C_7-CH_3	1.70 (d, *J* = 6.7 Hz)	1.70 (d, *J* = 7 Hz)	1.57 (d, *J* = 6.7 Hz)	
C_{10}-CH_3	1.60 (d, *J* = 6.6 Hz)	1.60 (d, *J* = 7 Hz)	1.5 (d, *J* = 6.7 Hz)	1.60 (d, *J* = 8.2 Hz)

Table 2
^{13}C-NMR data of compounds **15–20**

Signal	**15** and **16**	**17** and **18**	**19**	**20**
C_8 and C_5	166.1 and 160.4	165.8 and 160.1	166.1 and 160.3	165.1 and 160.4
C_{16b}	150.2	150.1	150.0	151.2
C_{17a} and C_{4a}	148,6 and 147.5	150.1 and 126.8	147.2 and 147.3	147.3 and 147.4
C_{10a} and C_{11a}	136.3 and 132.7	135.9 and 133.7	136.2 and 132.6	136.4 and 132.7
C_4	134.5	134.8	134.9	135.0
C_1	127.3	127.7	127.1	127.2
C_2	127.2	126.8	127.1	127.2
C_3	126.9	126.8	126.8	127.0
C_{15a}	126.4	126.2	126.3	126.4
C_{13}	122.6	122.5	122.4	122.5
C_{14}	120.1	120.1	120.4	120.0
C_{15}	118.6	118.1	118.4	118.5
C_{12}	111.11	111.0	111.0	111.1
C_{15b}	106.4	106.7	106.1	106.3
C_7	51.7	51.8	51.6	31.4
C_{16a}	52.8	54.1	52.6	52.9
C_{10}	46.1	45.5	46.0	46.3
C_{16}	31.0	29.6	31.8	26.7
C_{10}-CH_3 and C_7-CH_3	20.7 and 19.5	20.2 and 19.2	20.6 and 19.4	19.7

3.4. (3S,6R,12aR)-2-(o-Azidobenzoyl)-3,6-dimethyl-2,3,6,7,12,12a-hexahydropyrazino[1,2-b]-β-carboline-1,4-dione **21**

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 of 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 **6**[6] (100 mg, 0.35 mmol) in dry THF (20 ml) was dropwise added a 0.5 M solution of potassium hexamethyldisilazide in toluene (1.5 ml, 2.3 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 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 the residue was chromatographed on silica gel eluting with dichloromethane. Yield, 80 mg (53%) of compound **21**.

Data for **21**: Mp: 109–110°C. IR (KBr): 3368, 2130, 1722, 1655 and 1621 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.66 (s, 1H); 8.17 (d, 1H, *J*=8 Hz); 7–7.6 (m, 8H); 5.53 (q, 1H, *J*=6.4 Hz); 5.22 (q, 1H, *J*=7.3 Hz); 4.30 (dd, 1H, *J*=6.6 and 12.2 Hz); 3.61 (dd, 1H, *J*=4.7 and 15.6 Hz); 2.96 (dd, 1H, *J*=15.6 and 12.2 Hz); 1.57 (d, 3H, *J*=7.3 Hz); 1.52 (d, 3H, *J*=7.3 Hz) ppm. ^{13}C-NMR ($CDCl_3$) δ: 168.9; 168.8; 166.3; 137.5; 136.0; 134.9; 131.9; 129.2; 125.9; 125.2; 125.1; 123.9; 122.2; 120.0; 118.4; 118.1; 111.4; 105.8; 56.3; 53.9; 48.3; 23.4; 22.9; 17.1. $[\alpha]_D^{25}=-167$ (*c* 0.10, $CHCl_3$). Anal. calcd for $C_{23}H_{20}O_3N_6$: C, 64.48; H, 4.71; N,19.61. Found: C, 64.59; H, 4.76; N, 19.51.

3.5. Alternative synthesis of compound **18** by intramolecular aza-Wittig reaction of compound **21**

To a solution of compound **21** (81 mg, 0.187 mmol) in dry toluene (8 ml) was added tributylphosphine (80 μl, 0.35 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 (1:1) and then with ethyl acetate. Yield, 15 mg (21%) of compound **18**.

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