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# Steric and stereochemical effects on the free-radical bromination of tetracyclic and hexacyclic fragments of the MDR inhibitor *N*-acetylardeemin

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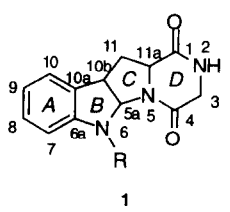
***Abstract***. The bromination of several tetracyclic 3,5a,6,10b,11,11a-hexahydro-2*H*-pyrazino[2',1'-5,1]pyrrolo[2,3-*b*]indole-1,4-diones under free radical conditions was studied. In contrast with literature data for related pyrrolo[2,3-*b*]indole derivatives, the reaction occurs normally at the 11a position rather than at the benzylic 10b position and was followed by elimination, leading to 11,11a unsaturated derivatives. Compounds with an increased steric hindrance at 11a afforded *B-C* ring aromatized derivatives. Hexacyclic derivatives of the 7,9a,10,14b,15,15a-hexahydroindolo[3",2"-4',5']pyrrolo[2',1'-3,4]-pyrazino[2,1-*b*]quinazoline-5,8-dione system showed a behaviour similar to the 'non-hindered' tetracycles, leading to unsaturated analogues of the natural MDR inhibitor *N*-acetylardeemin. Unsaturated ardeemin analogues were also obtained by bromination of 2-(*o*-azidobenzoyl) derivatives of the tetracyclic systems followed by aza-Wittig cyclization. 

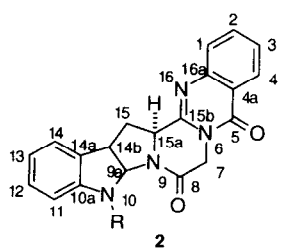
*Keywords*: Quinazolinones, piperazinones, radicals and radical reactions, elimination reactions, Wittig reactions.

## 1. Introduction

The 3,5a,6,10b,11,11a-hexahydro-2*H*-pyrazino[2',1'-5,1]pyrrolo[2,3-*b*]indole-1,4-dione system (**1**) is a fragment of the structure of *N*-acetylardeemin,[1] a potent inhibitor of multi-drug resistance to antitumour agents (MDR),[2] and is also present in other natural products, like the fructigenines[3] and the roquefortines.[4] The related 7,9a,10,14b,15,15a-hexahydroindolo[3",2"-4',5']pyrrolo[2',1'-3,4]-pyrazino[2,1-*b*]quinazoline-5,8-dione structure (**2**) contains the complete ring system of *N*-acetylardeemin. As part of our current work on the synthesis of analogues of this natural product,[5,6] we became interested in studying the bromination of structures **1** and **2** under free radical conditions.




**1**




**2**

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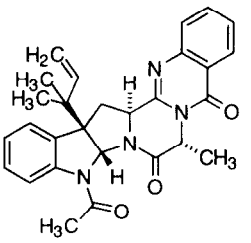
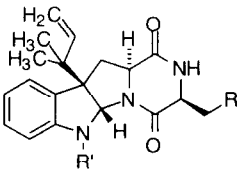
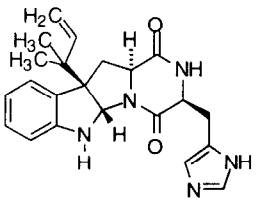


*N*-Acetylardeemin



R = $C_6H_5$ (fructigenine A)
R = $CH(CH_3)_2$ (fructigenine B)



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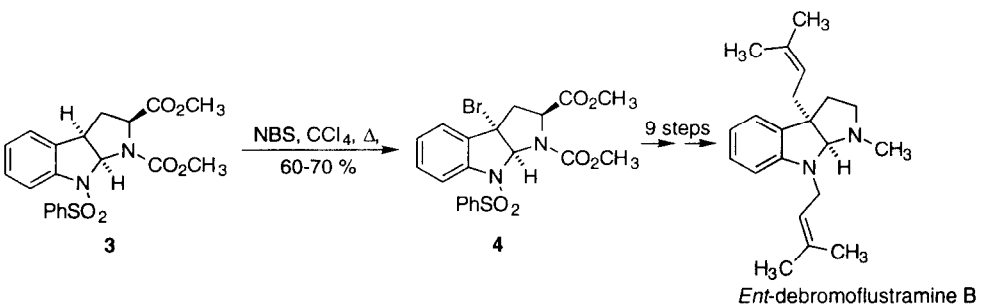
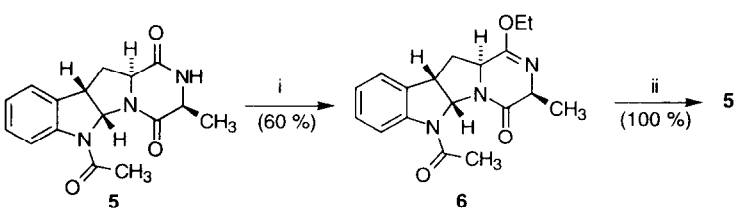
The closest literature precedent to our proposed reactions was investigated in the context of a total synthesis of (+)-*ent*-debromoflustramine B by the Crich group.[7] It consists of the reaction between the pyrrolo[2,3-*b*]indole derivative **3** and *N*-bromosuccinimide in carbon tetrachloride, which led to regio- and stereo- selective bromination at the benzylic position and afforded compound **4** in 60-70 % yield (Scheme 1).




Scheme 1

## 2. Results and discussion

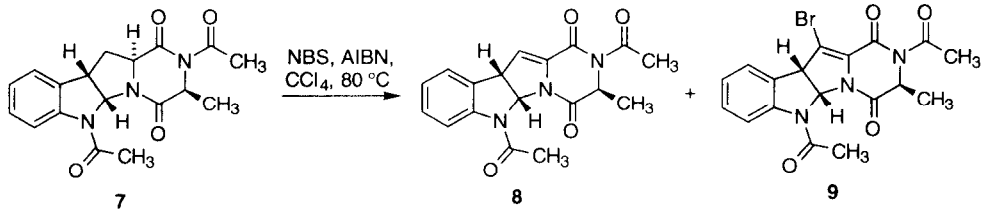
Our first attempts at the bromination of pyrazino[2',1'-5,1]pyrrolo[2,3-*b*]indole-1,4-dione derivatives were carried out on compound **5**,[5a] but its low solubility in carbon tetrachloride precluded the desired reaction. Since previous work[7] had stressed the importance of using this solvent in order to avoid bromination of the indole system, we decided to increase the solubility of compound **5** by transformation into the corresponding iminoether (compound **6**). However, all attempts to brominate **6** with NBS/AIBN failed and the only isolated product was **5**, from cleavage of **6** (Scheme 2). This easy hydrolysis can be ascribed to the formation of catalytic amounts of hydrobromic acid from *N*-bromosuccinimide.




**Reagents and conditions**: i. $Et_3O^+$ $BF_4^-$, $Na_2CO_3$, $CH_2Cl_2$, r.t., 24 h. ii. NBS, AIBN, $CCl_4$, 80 °C, 4 h

Scheme 2

An alternative derivative of the parent structure with increased solubility is the 2-acetyl derivative **7**.[5a] Treatment of this compound with NBS/AIBN in refluxing carbon tetrachloride for 1 h afforded a 43 % yield of the *C*-ring unsaturated compound **8**. Forcing conditions (excess NBS, 20 h reaction time) led to a similar yield of **8**, together with 12 % of its bromo derivative **9** (Scheme 3).

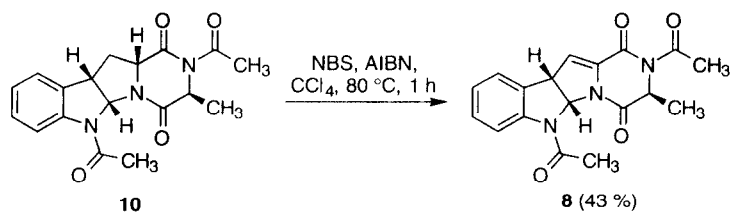



**7** **8** **9**

| Time | % **8** | % **9** |
|---|---|---|
| 1 h | 43 | 0 |
| 20 h | 43 | 12 |

Scheme 3

These results are in contrast with the behaviour described by Crich and suggest an initial reaction at the 11a carbon rather than at the benzylic position (see below). Since the different reactivity might be due to stereochemical differences between our substrate and the one used by Crich, we were prompted to study the influence of stereochemical factors on the outcome of the free-radical bromination. In order to examine the possible influence of the configuration of the tryptophan stereocenter, we treated compound **10**[5a] with NBS/AIBN for 1 h. As shown in Scheme 4, the result we obtained was identical to the one observed starting from its epimer **7** (43 % yield of compound **8**).

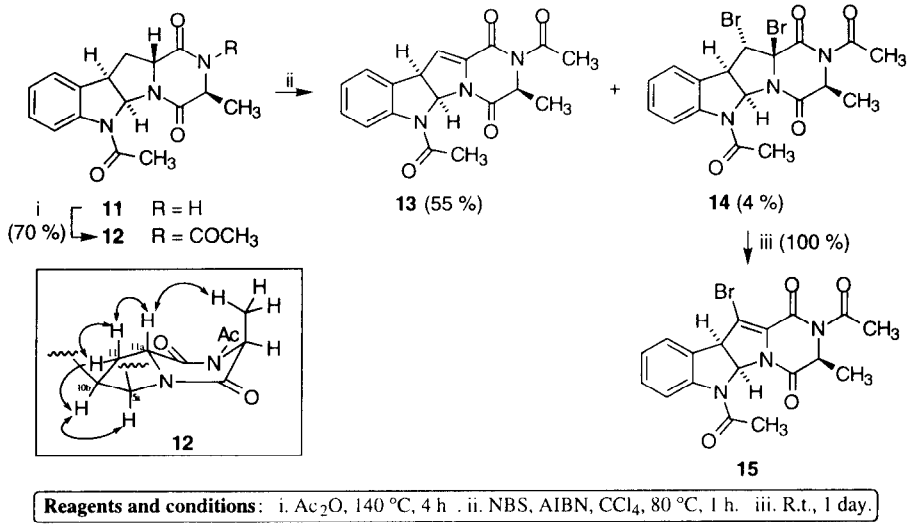



**10** **8** (43 %)

Scheme 4

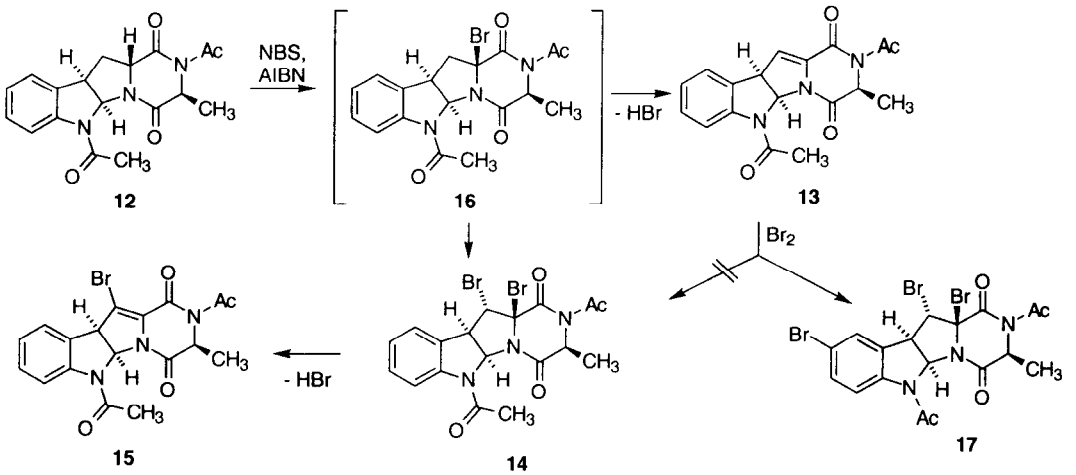
Compound **11**[5a] contains a third combination of the stereocenters in the tetracyclic system. Its acetylation with refluxing acetic anhydride for 4 h afforded compound **12** in 70 % yield (the absence of epimerization during the synthesis of **12** was confirmed through the NOE study summarized in Scheme 5). When **12** was submitted to the usual bromination conditions, the main product (55 % yield) was again the 11-11a unsaturated derivative (compound **13**), together with a small amount (4 %) of the dibromo compound **14** (Scheme 5). The configuration of the 11 and 11a stereocenters of **14** was proposed on the basis of the lack of coupling between the 10b and 11 protons, which shows that the C10b-H and C11-H bonds are perpendicular,[8] and on the *trans* stereochemistry expected for the bromine atoms. Compound **14** was unstable, and was quantitatively transformed into the unsaturated bromo derivative **15** upon storage at room temperature for 1 day through

elimination of HBr, probably assisted by the neighbouring N-9 atom. The latter reaction served also to confirm the structure of **14**.



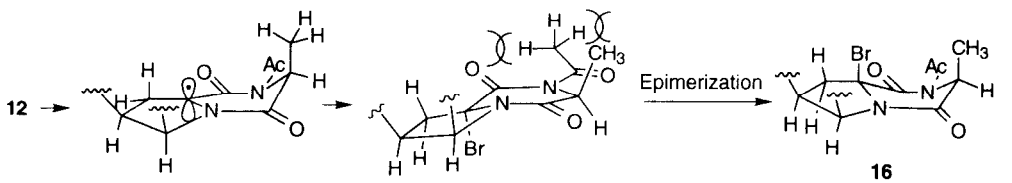

Scheme 5

A mechanism that accounts for our observations is summarized in Scheme 6, using **12** as the starting compound. Taking into account that formation of a free radical at the position adjacent to the tryptophan carbonyl (C-11a) is favoured owing to captodative stabilization,[9] our results suggest that the substitution reaction takes place at the tryptophan stereocenter rather than at the benzylic position,[10] leading to the non-isolated compound **16**. Elimination of HBr from **16** accounts for the formation of enamide **13**, an observation that suggests a similar origin for the above mentioned compound **8**.




Scheme 6

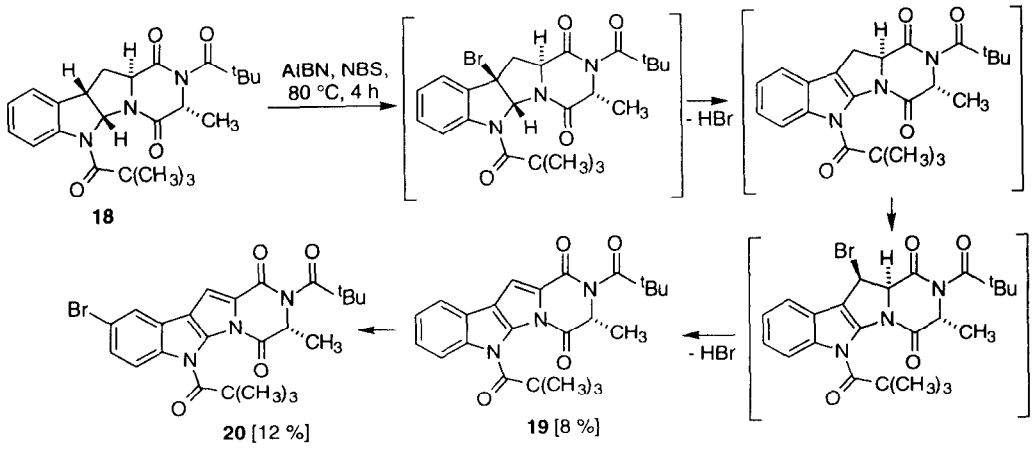
Regarding the formation of the dibromo derivative **14**, the literature contains some examples of reactions of α-aminoacids[11] or 3-alkyl-2,5-piperazinediones[12] with NBS/AIBN that have afforded similar dibromo derivatives. Their formation has normally been explained through addition of bromine to a dehydro derivative similar to our compound **13**, arising from HBr elimination from the initial monobrominated derivative of the starting material. In an attempt to check this assumption, we treated isolated **13** with NBS under the conditions employed for **12**, but this reaction led only to recovered starting material, and the use of forcing conditions afforded mixtures of starting **13** and the tribrominated compound **17**; the structure of the latter was independently confirmed through its preparation in 80 % yield from **13** and excess bromine. Therefore, we suggest that **14** does not arise from **13**, but from a second bromination of **16**, a proposal supported by the fact that bromination of alkyl bromides occurs preferentially at a carbon atom α to the bromine initially present in the substrate.[13] Since this neighbouring group assistance requires the formation of a cyclic intermediate where the second bromine atom is introduced opposite to the first,[13] the stereochemistry proposed for **14** requires the structure **16** shown in Scheme 5 for the non-isolated monobrominated derivative. Although the α face of the intermediate radical is undoubtedly less hindered than the β face, the 11a α-bromo derivative would be destabilized by the repulsive interactions between the C(1)=O, N(2)-Ac and C(3)-Me groups. Epimerization at 11a, which is possible under the reaction conditions,[14] would alleviate this problem, as confirmed by MM2 calculations. This epimerization would explain the formation of the postulated intermediate **16** (Scheme 7).




Scheme 7

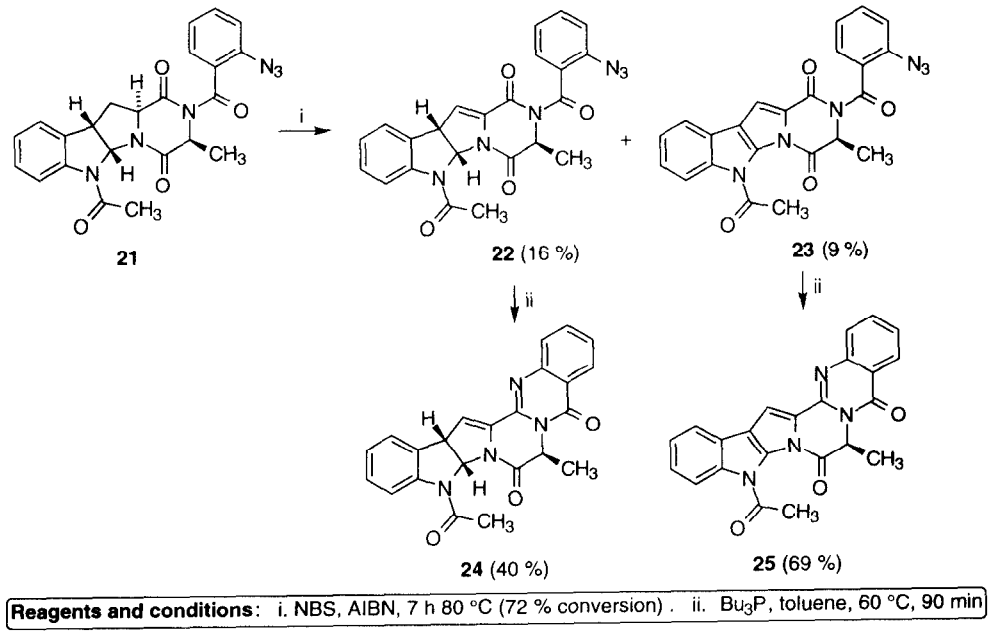
We next decided to examine the dipivaloyl derivative **18**[5a] as the substrate for the radical bromination. This compound shows an increased steric hindrance at the tryptophan stereocenter because of the very bulky substituent at N-2 and the pseudoaxial orientation of its C-3 methyl group, and hence it was a good substrate on which to study the possibility of achieving benzylic bromination. As shown in Scheme 8, and according to our expectations, bromination at C-11a was indeed more difficult, and the only products that could be isolated were the *B*- and *C*-ring aromatized compounds **19** (8 %) and **20** (12 %), whose formation must involve free-radical bromination at the benzylic C-10b position. Although it is not possible to determine unequivocally whether this process took place on the starting material **18** or on a non-isolated intermediate with a 11,11a double bond similar to compound **8**, the fact that this aromatization has been observed only in the case where C-11a is hindered suggests that benzylic bromination was the initial reaction, followed by elimination, a second benzylic bromination and a new elimination. Finally, aromatic bromination of **19** explains the isolation of **20**.

At this point, we turned our attention to the application of this chemistry to the synthesis of unsaturated analogues of *N*-acetylardeemin. With this purpose, we decided to study the halogenation of 2-(*o*-azidobenzoyl) derivatives of the tetracyclic system, which are precursors of the hexacyclic compounds through aza-Wittig reactions.[1c,5b] Thus, compound **21**, upon treatment with NBS/AIBN, showed a behaviour intermediate between that of 'non-hindered' tetracyclic systems (*e.g.* compounds **7**, **10** and **12**, Schemes 3-5) and 'hindered' ones




Scheme 8

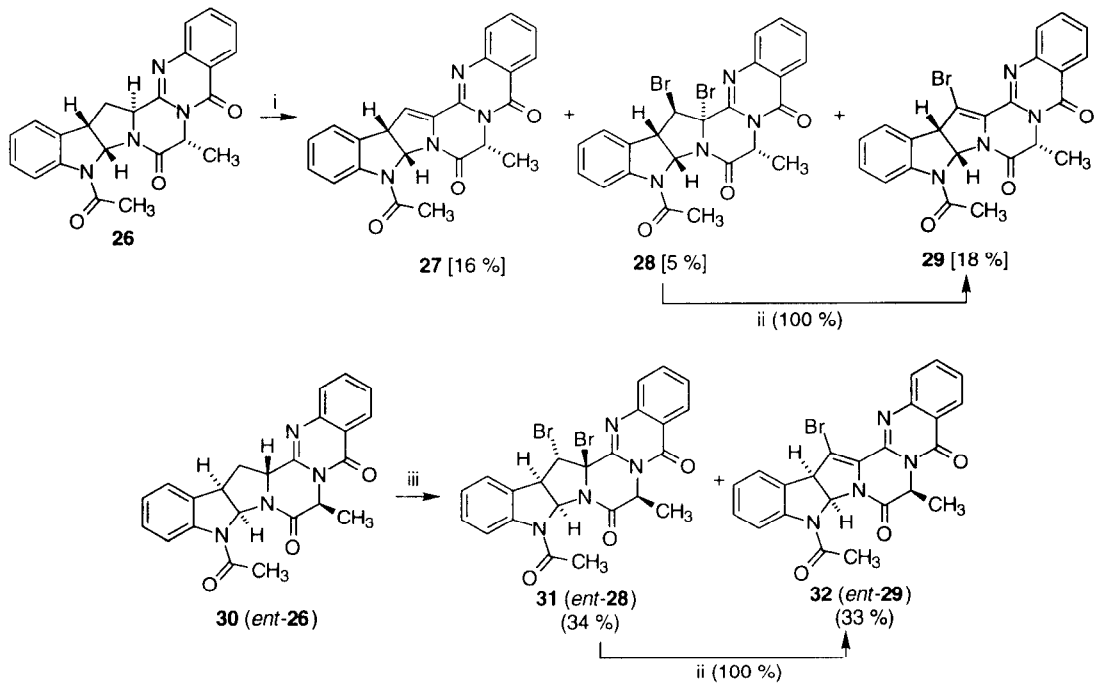
(*e.g.* compound **18**, Scheme 8), since it afforded a mixture of the enamide **22** and the aromatic system **23**, both in low yields. Their treatment with tributylphosphine gave the hexacyclic compounds **24** and **25**, respectively (Scheme 9).




Scheme 9

Finally, we decided to examine the bromination reactions of hexacyclic compounds containing the complete ring system of ardeemine. The reaction of compound **26**[5b] with NBS/AIBN was sluggish, probably owing to the steric hindrance due to the pseudoaxial orientation of the methyl group, and gave only 64 % conversion after a 7 h reflux. The main reaction products were compounds **27** and **29**, together with a small amount of the

unstable dibromo intermediate **28**. The course of the reaction was slightly different to the one observed for the non-hindered tetracyclic systems in that it follows the two possible pathways outlined in Scheme 6. In an attempt to establish the order in which these two pathways took place initially while at the same time increasing the structural variation for biological studies, we carried out a similar reaction for 4 h on compound **30**, the enantiomer of **26**. This reaction led to a mixture of the dibromo intermediate **31** (*ent*-**28**) and the corresponding bromoenamide **32** (*ent*-**29**), but not to the enantiomer of enamide **27** (Scheme 10). This result shows that, at least in the case of the hexacyclic derivatives **26** and **30**, elimination of HBr from the monobrominated derivative proposed as the first reaction intermediate is hampered, probably because of steric interference on the leaving group.




**Reagents and conditions**: i. NBS, AIBN, $CCl_4$, 80 °C, 7 h (64 % conversion). ii. R.t., 1 day. iii. NBS, AIBN, $CCl_4$, 80 °C, 4 h (62 % conversion).

Scheme 10

In summary, our results show that 2-acylpyrazino[2',1'-5,1]pyrrolo[2,3-*b*]indole-1,4-diones are brominated at the 11a position under free radical conditions, and that the halogenated derivative thus formed undergoes a rapid elimination to give a 11,11a double bond or, alternatively, a second bromination at C-11 followed by elimination. Bromination at the benzylic 10b position, which is the main reaction in the case of related, simpler pyrrolo[2,3-*b*]indole derivatives, takes place only when the 11a position is very hindered. Related hexacyclic hexahydroindolo[3",2"-4',5']pyrrolo[2',1'-3,4]-pyrazino[2,1-*b*]-quinazoline-5,8-dione derivatives react also at the tryptophan stereocenter.

## 3. Experimental

All reagents were of commercial quality (Aldrich, Fluka, SDS, Probus) and were used as received. Solvents (SDS) were dried and purified using standard techniques. Petroleum ether refers to the fraction boiling at 40-60 °C. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (Macherey-Nagel Alugram Sil G/$UV_{254}$). Separations by flash chromatography were performed on silica gel (SDS 60 ACC, 230-400 mesh). Melting points were measured in open capillary tubes using a Reichert 723 hot stage microsope, and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrophotometer, with all compounds examined as films on a NaCl disk. NMR spectra were obtained on a Bruker AC-250 spectrometer (250 MHz for $^1H$, 63 MHz for $^{13}C$), with $CDCl_3$ as solvent (Servicio de Espectroscopía, Universidad Complutense). When necessary, assignments were aided by HOMO decoupling, DEPT and COSY experiments. Mass spectra were obtained by the Servicio de Espectroscopía, Universidad Complutense, on a Hewlett-Packard 5989A spectrometer using the electron impact mode, with the exception of compound **14**, for which chemical ionization with methane was also employed. High resolution mass measurements were obtained by the Servicio Central de Soporte a la Investigación Experimental (Universidad de Valencia) on a UG Autospec spectrometer. 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.

### *3.1. Reaction of compound 7 with NBS/AIBN.*

A solution of compound **7**[8] (28 mg, 0.082 mmol), AIBN (1.35 mg, 0.0082 mmol) and NBS (14.60 mg, 0.082 mmol) in carbon tetrachloride (10 ml) was refluxed in an oil bath at 80 °C for 1 h, under an inert atmosphere. The reaction mixture was cooled, and a precipitate of succinimide was filtered off and washed with carbon tetrachloride (2 x 5 ml). Evaporation of the combined filtrates gave a residue, which was purified by column chromatography on silica gel, eluting with 1.5:1 petroleum ether-ethyl acetate, yielding 12 mg (43 %) of compound **8** as pale yellow crystals. When the reflux was prolonged for 7 h, the yields were 12 mg (43 %) of compound **8** and 4 mg (12 %) of compound **9**, as pale yellow crystals.

Data for **8**: mp 65-68 °C. IR (NaCl): 1706.3 (CO) $cm^{-1}$. $^1H$-NMR ($CDCl_3$): δ 8.05 (d, 1H, $J$ = 8.0 Hz, H-7); 7.26 (m, 2H, H-8,10); 7.12 (t, 1H, $J$ = 7.4 Hz, H-9); 6.78 (d, 1H, $J$ = 8.0 Hz, H-5a); 6.53 (d, 1H, $J$ = 2.8 Hz, H-11), 5.10 (q, 1H, $J$ = 7.1 Hz, H-3); 4.89 (br. d, 1H, $J$ = 8.0 Hz, H-10b); 2.67 (s, 3H, $N_6$-Ac); 2.48 (s, 3H, $N_2$-Ac); 1.51 (d, 3H, $J$ = 7.1 Hz, $C_3$-$CH_3$). $^{13}C$-NMR ($CDCl_3$): δ 171.28 and 171.14 ($COCH_3$); 167.02 (C-1); 158.03 (C-4); 142.06 (C-6a); 134.21 (C-11a); 129.34 (C-10a); 128.95 (C-9); 125.13 (C-8); 124.09 (C-10); 122.40 (C-11); 119.32 (C-7); 78.73 (C-5a); 54.28 (C-3); 50.16 (C-10b); 26.61 ($N_2$-CO-$CH_3$); 24.35 ($N_6$-CO-$CH_3$); 20.60 ($C_3$-$CH_3$). MS, *m/z* (%): 339 (10, $M^+$); 297 (100, $M^+$ - Ac); 255 (95, $M^+$ - 2 Ac). $[\alpha]_D^{25}$ -13.3 (0.255, $CHCl_3$). Anal. calcd. for $C_{18}H_{17}N_3O_4$: C, 63.72; H, 5.01; N, 12.39. Found: C, 63.44, H, 5.02; N, 12.03.

Data for **9**: mp 94-95 °C. IR (NaCl): 1697.7 (CO); 1242.7 (*C*=*C*-Br); 744 (=*C*-*Br*) $cm^{-1}$. $^1H$-NMR ($CDCl_3$): δ 8.06 (d, 1H, $J$ = 8.3 Hz, H-7); 7.62 (d, 1H, $J$ = 7.6 Hz, H-10); 7.36 (t, 1H, $J$ = 6.8 Hz, H-8); 7.16 (t, 1H, $J$ = 7.5 Hz, H-9); 6.79 (d, 1H, $J$ = 8.2 Hz, H-5a); 5.12 (q, 1H, $J$ = 7.2 Hz, H-3); 4.89 (d, 1H, $J$ = 8.1

Hz, H-10b); 2.58 (s, 3H, $N_6$-Ac); 2.51 (s, 3H, $N_2$-Ac); 1.53 (d, 3H, $J$ = 7.2 Hz, $C_3$-$CH_3$). MS, *m/z* (%): 419 (8, $M^+$, $^{81}Br$) and 417 (8, $M^+$, $^{79}Br$); 377 (100, $M^+$ - Ac, $^{81}Br$); 375 (94, $M^+$ - Ac, $^{79}Br$); 335 (29, $M^+$ - Br); 296 (59, $M^+$ - Br - Ac); 254 (83, $M^+$ - Br - 2Ac). HRMS: Calcd. for $C_{18}H_{16}BrN_3O_4$ ($M^+$, $^{81}Br$): 419.0304. Found: 418.9753. Calcd. for $C_{16}H_{14}BrN_3O_3$ ($M^+$ - Ac, $^{81}Br$): 377.0199. Found: 377.0292 $[\alpha]_D^{25}$ -30.0 (0.04, $CHCl_3$).

*3.2. Reaction of compound **10** with NBS/AIBN.*

A solution of compound **10**[8] (28 mg, 0.082 mmol), AIBN (1.35 mg, 0.0082 mmol) and NBS (14.60 mg, 0.082 mmol) in carbon tetrachloride (10 ml) was treated as indicated in section 3.1, yielding 12 mg (43 %) of compound **8**.

*3.3. Acetylation of compound **11**.*

A solution of compound **11** (76 mg, 0.25 mmol) in acetic anhydride (10 ml) was refluxed in an oil bath at 140 °C for 4 h. The solution was cooled and evaporated, and the residue was purified by column chromatography on silica gel, eluting with ethyl acetate, yielding 87 mg (70 %) of compound **12** as white crystals, mp 76-78 °C. IR (NaCl): 1679.3 (CO) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 8.00 (d, 1H, $J$ = 7.7 Hz, H-7); 7.28 (m, 2H, H-9,10); 7.15 (td, 1H, $J$ = 7.6 and 0.7 Hz, H-8); 6.30 (d, 1H, $J$ = 6.1 Hz, H-5a); 5.02 (q, 1H, $J$ = 7.1 Hz, H-3); 4.17 (t, 1H, $J$ = 6.3 Hz, H-10b); 4.06 (dd, 1H, $J$ = 11.1 and 5.9 Hz, H-11a); 2.83 (dd, 1H, $J$ = 12.9 and 5.9 Hz, H-11); 2.66 (s, 3H, $N_6$-Ac); 2.52 (s, 3H, $N_2$-Ac); 2.42 (m, 1H, H-11); 1.35 (d, 3H, $J$ = 7.1 Hz, $C_3$-$CH_3$). $^{13}$C-NMR ($CDCl_3$): δ 171.25 and 170.55 ($COCH_3$); 168.73 (C-1); 166.45 (C-4); 142.73 (C-6a); 130.41 (C-10a); 129.04 (C-9); 125.16 (C-8); 123.59 (C-10); 119.24 (C-7); 58.78 (C-11a); 54.88 (C-3); 44.05 (C-10b); 34.81 (C-11); 27.54 ($N_2$-CO-$CH_3$); 23.82 ($N_6$-CO-$CH_3$); 18.02 ($C_3$-$CH_3$). $[\alpha]_D^{25}$ -79.0 (0.20, $CHCl_3$). Anal. calcd. for $C_{18}H_{19}N_3O_4$: C, 63.34; H, 5.57; N, 12.32. Found: C, 63.11; H, 5.83; N, 12.52.

*3.4. Reaction of compound **12** with NBS/AIBN.*

A solution of compound **12** (130 mg, 0.38 mmol), AIBN (6.26 mg, 0.038 mmol) and NBS (67.8 mg, 0.38 mmol) in carbon tetrachloride (10 ml) was treated as indicated in section 3.1. Column chromatography on silica gel, eluting with 2:1 petroleum ether-ethyl acetate, afforded compound **13** as pale yellow crystals (70 mg, 55 %), the unstable compound **14** (7 mg, 4 %), as an oil that was quantitatively transformed into the unsaturated bromo derivative **15** upon standing at room temperature for 1 day,[15] and 52 mg (40 %) of recovered starting material.

Data for **13**: mp 155-157 °C. IR (NaCl): 1682.2 (CO) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 7.97 (d, 1H, $J$ = 7.7 Hz, H-7); 7.36 (m, 2H, H-8,10); 7.17 (t, 1H, $J$ = 7.6 Hz, H-9); 6.79 (d, 1H, $J$ = 6.6 Hz, H-5a); 5.39 (d, 1H, $J$ = 2.9 Hz, H-11), 5.15 (q, 1H, $J$ = 7.1 Hz, H-3); 4.81 (d, 1H, $J$ = 6.7 Hz, H-10b); 2.68 (s, 3H, $N_6$-Ac); 2.59 (s, 3H, $N_2$-Ac); 1.64 (d, 3H, $J$ = 7.1 Hz, $C_3$-$CH_3$). $^{13}$C-NMR ($CDCl_3$): δ 171.44 and 170.87 ($COCH_3$); 166.76 (C-1); 162.71 (C-4); 143.70 (C-6a); 130.92 (C-11a); 129.67 (C-9); 128.80 (C-10a); 125.36 (C-8); 124.37 (C-10); 119.66 (C-7); 119.22 (C-11); 78.91 (C-5a); 57.56 (C-10b); 55.11 (C-3); 27.60 ($N_2$-CO-$CH_3$);

25.27 ($N_6$-CO-$CH_3$); 17.28 ($C_3$-$CH_3$). $[\alpha]_D^{25}$ -24.0 (0.05, EtOH). Anal. Calcd. for $C_{18}H_{17}N_3O_4$: C, 63.72; H, 5.01; N, 12.39. Found: C, 63.51; H, 4.85; N, 12.12.

Data for **14**: $^1$H-NMR ($CDCl_3$): δ 8.03 (d, 1H, *J* = 8.2, H-7); 7.64 (d, 1H, *J* = 7.6 Hz, H-10); 7.37 (t, 1H, *J* = 7.9 Hz, H-8); 7.18 (t, 1H, *J* = 7.5 Hz, H-9); 6.68 (d, 1H, *J* = 8.4 Hz, H-5a); 5.30 (s, 1H, H-11); 4.99 (q, 1H, *J* = 7.0 Hz, H-3); 4.75 (d, 1H, *J* = 8.3, H-10b); 2.63 (s, 3H, N6-Ac); 2.56 (s, 3H, N2-Ac); 1.30 (d, 3H, *J* = 7.1 Hz, $C_3$-$CH_3$). Anal. calcd. for $C_{18}H_{17}Br_2N_3O_4$: C, 43.31; H, 3.43; N, 8.42. Found: C, 42.92, H, 3.61; N, 8.72. These data were obtained obtained immediately after purification of **14**; otherwise, the microanalytical data obtained correspond to those expected for compound **15** (see note 15).

Data for **15** (pale yellow crystals): mp 75-77 °C. IR (NaCl): 1701.5 (CO); 757.8 (C-Br) cm$^{-1}$. $^1$H-NMR ($CDCl_3$): δ 8.05 (d, 1H, *J* = 8.2, H-7); 7.65 (d, 1H, *J* = 7.5 Hz, H-10); 7.37 (t, 1H, *J* = 7.9 Hz, H-8); 7.18 (t, 1H, *J* = 7.5 Hz, H-9); 6.68 (d, 1H, *J* = 8.3 Hz, H-5a); 4.99 (q, 1H, *J* = 7.0 Hz, H-3); 4.75 (d, 1H, *J* = 8.2, H-10b); 2.63 (s, 3H, $N_6$-Ac); 2.56 (s, 3H, $N_2$-Ac); 1.31 (d, 3H, *J* = 7.0 Hz, $C_3$-$CH_3$). MS, *m/z* (%): 419 (6, $M^+$, $^{81}$Br) and 417 (5, $M^+$, $^{79}$Br); ); 377 (74, $M^+$ - Ac, $^{81}$Br) and 375 (75, $M^+$ - Ac, $^{79}$Br); 338 (25, $M^+$ - Br); 296 (54, $M^+$ - Br - Ac); 254 (100, $M^+$ - Br - 2 Ac). Anal. calcd. for $C_{18}H_{16}BrN_3O_4$: C, 51.55; H, 3.82; N, 10.02. Found: C, 51.82, H, 3.95; N, 9.75.

### *3.5. Reaction of compound 13 with bromine or NBS.*

To a solution of compound **13** (47 mg, 0.139 mmol) in $CCl_4$ (10 ml) was added bromine (20 µl, 2.5 eq) and AIBN (2 mg, 0.1 eq). The solution was refluxed in an oil bath at 80 °C for 4 h, under an inert atmosphere. The reaction mixture was cooled, and the precipitated pale yellow solid was filtered and identified as compound **17** (64 mg, 80 %). When a similar reaction was carried out from **13** and *N*-bromosuccinimide, a 3:1 mixture of starting material and compound **17** was recovered, after 7 h at 80 °C.

Data for **17**: mp 161-163 °C. IR (NaCl): 1714.4 (CO); 730.3 (C-Br) cm$^{-1}$. $^1$H-NMR ($CDCl_3$): δ 7.91 (d, 1H, *J* = 8.6, H-7); 7.54 (d, 1H, *J* = 1.5 Hz, H-10); 7.47 (dd, 1H, *J* = 8.6 and 1.6 Hz, H-8); 6.76 (d, 1H, *J* = 6.7 Hz, H-5a); 5.36 (s, 1H, H-11); 5.17 (q, 1H, *J* = 7.2 Hz, H-3); 4.79 (d, 1H, *J* = 6.6 Hz, H-10b); 2.69 (s, 3H, $N_6$-Ac); 2.61 (s, 3H, $N_2$-Ac); 1.66 (d, 3H, *J* = 7.2 Hz, $C_3$-$CH_3$). MS, *m/z* (%): 377 (10), 375 (10) ($M^+$ - 2 Br); 335 (24), 333 (24) ($M^+$ - 2 Br - 2 Ac). MS (CI), *m/z* (%): 500 (15), 498 (25), and 496 (15) ($M^+$ - Br). $[\alpha]_D^{25}$ + 214.5 (0.145, $CHCl_3$). Anal. Calcd. for $C_{18}H_{16}Br_3N_3O_4$: C, 37.37; H, 2.77; N, 7.27. Found: C, 37.48; H, 3.13; N, 6.97.

### *3.6. Reaction of compound 18 with NBS/AIBN.*

A solution of compound **18** [8] (144 mg, 0.34 mmol), AIBN (55.6 mg, 0.034 mmol) and NBS (72.6 mg, 0.41 mmol) in carbon tetrachloride (10 ml) was refluxed in an oil bath at 80 °C for 4 h, under an inert atmosphere. The reaction mixture was cooled, and a precipitate of succinimide was filtered off and washed with carbon tetrachloride (2 x 5 ml). Evaporation of the combined filtrates gave a residue, which was purified by column chromatography on silica gel, eluting with 4:1 petroleum ether-ethyl acetate. Yield, 10 mg (8 %) of compound **19**, as off-white crystals, 20 mg (12 %) of compound **20** as pale yellow crystals, and 43 mg (30 %) of recovered starting material.

Data for **19**: mp 89-90 °C. IR (NaCl): 1667.0 (CO) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 8.11 (d, 1H, *J* = 8.2 Hz, H-7); 7.61 (d, 1H, *J* = 1.6 Hz, H-11); 7.39 (m, 2H, H-8,10); 7.20 (t, 1H, *J* = 7.0 Hz, H-9); 5.01 (q, 1H, *J* = 7.0 Hz, H-3); 1.72 (d, 3H, *J* = 7.0 Hz, $C_3$-$CH_3$); 1.37 and 1.25 (2 s, each 9H, Piv). MS, *m/z* (%): 421 (5, $M^+$); 337 (16, $M^+$ - Piv); 253 (10, $M^+$ - 2 Piv); 57 (100, *t*-Bu). $[\alpha]_D^{25}$ + 1.2 (0.325, $CHCl_3$). Anal. calcd. for $C_{24}H_{27}N_3O_4$: C, 68.41; H, 6.41; N, 9.98. Found: C, 68.68, H, 6.18; N, 9.73.

Data for **20**: 79-80 °C. IR (NaCl): 1666.8 (CO); 1228.6 (*C*=*C*-Br); 756 (=*C*-*Br*) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 8.04 (d, 1H, *J* = 7.2 Hz, H-7); 7.61 (d, 1H, *J* = 1.7 Hz, H-11); 7.49 (dd, 1H, *J* = 7.3 and 2.0 Hz, H-8); 7.34 (d, 1H, *J* = 1.7 Hz, H-10); 5.00 (q, 1H, *J* = 7.0 Hz, H-3); 1.71 (d, 3H, *J* = 7.0 Hz, $C_3$-$CH_3$); 1.37 (s, 9H, $N_6$-Piv); 1.23 (s, 9H, $N_2$-Piv). MS, *m/z* (%): 417 (10, $M^+$ - Piv, $^{81}$Br); 415 (11, $M^+$ - Piv, $^{79}$Br); 85 (13, Piv); 57 (100, *t*-Bu). $[\alpha]_D^{25}$ + 1.8 (0.325, $CHCl_3$). Anal. Calcd. for $C_{24}H_{26}BrN_3O_4$: C, 57.60; H, 5.20; N, 8.40. Found: 57.40; H, 4.97; N, 8.22.

*3.7. Reaction of compound **21** with NBS/AIBN.*

A solution of compound **21** (100 mg, 0.226 mmol), AIBN (3.72 mg, 0.023 mmol) and NBS (48.28 mg, 0.271 mmol) in carbon tetrachloride (10 ml) was refluxed for 7 h and treated as in section 3.1. Chromatography on silica gel, eluting with 6:1 petroleum ether-ethyl acetate afforded 16 mg (16 %) of compound **22** as white crystals, 9 mg (9 %) of compound **23** as a pale yellow oil and 28 mg (28 %) of recovered **21**.

Data for **22**: mp 78 °C. IR (NaCl): 2129.5 ($N_3$); 1710.1 (CO) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 8.06 (d, 1H, *J* = 8.1 Hz, H-7); 7.44 (m, 2H, H-5',6'); 7.28 (t, 1H, *J* = 7.3 Hz, H-9); 7.14 (m, 3H, H-4',8,10); 7.03 (d, 1H, *J* = 8.0 Hz, H-3'); 6.82 (d, 1H, *J* = 8.0 Hz, H-5a); 6.50 (d, 1H, *J* = 3.0 Hz, H-11); 5.11 (q, 1H, *J* = 7.2 Hz, H-3); 4.88 (dd, 1H, *J* = 7.9 and 3.0 Hz, H-10b); 2.72 (s, 3H, $N_6$-Ac); 1.66 (d, 3H, *J* = 7.1 Hz, $C_3$-$CH_3$). $^{13}$C-NMR ($CDCl_3$): δ 170.95 (*C*$OCH_3$); 167.40 (C-1); 166.97 (C-4); 165.97 (CO-Ar); 141.77 (C-6a); 136.78 (C-10a); 133.96 (C-11a); 132.15 (C-5'); 129.52 (C-2'); 129.63 (C-3'); 128.99 (C-1'); 127.00 (C-9); 125.23 and 125.11 (C-6' and C-8); 124.01 (C-10); 122.46 (C-11); 119.51 (C-4'); 118.23 (C-7); 78.76 (C-5a); 55.23 (C-3); 50.11 (C-10b); 24.29 (CO-*C*$H_3$); 20.66 ($C_3$-$CH_3$). $[\alpha]_D^{25}$ - 25.0 (0.14, $CHCl_3$). Anal. calcd. for $C_{23}H_{18}N_6O_4$: C, 62.44; H, 4.07; N, 19.00. Found: C, 62.14, H, 3.85; N, 18.85.

Data for **23**: IR (NaCl): 2129.4 ($N_3$); 1682.0 (CO) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 8.11 (d, 1H, *J* = 7.9 Hz, H-7); 7.78 (d, 1H, *J* = 7.0, H-10); 7.64 (s, 1H, H-11); 7.48 (m, 4H, H-3',5',6',9); 7.23 (m, 2H, H-4',8); 5.58 (q, 1H, *J* = 7.1 Hz, H-3); 2.71 (s, 3H, $N_6$-Ac); 1.79 (d, 3H, *J* = 7.0 Hz, $C_3$-$CH_3$). $^{13}$C-NMR ($CDCl_3$): δ 169.25 (*C*$OCH_3$); 167.94 (C-1); 167.46 (C-4); 163.55 ($N_2$-*C*O-Ar); 140.95 (C-6a); 136.76 (C-10a); 135.71 (C-5a); 132.57 (C-5'); 131.80 (C-3'); 128.54 (C-1'); 126.28 (C-9); 125.42 (C-2'); 125.17 (C-6'); 124.77 (C-8); 124.63 (C-10); 121.38 (C-11a); 56.07 (C-3); 27.02 ($N_6$-CO-*C*$H_3$); 21.03 ($C_3$-$CH_3$). $[\alpha]_D^{25}$ + 41.2 (0.17, $CHCl_3$). MS, *m/z* (%): 442 (6, $M^+$); 398 (48, $M^+$ - Ac); 253 (87, $M^+$ - CO-Ar). Anal. Calcd. for $C_{23}H_{16}N_6O_4$: C, 62.72; H, 3.63; N, 19.09. Found: C, 62.51; H, 3.47; N, 18.95.

*3.8. Aza-Wittig cyclizations of compounds **22** and **23**.*

A solution of the suitable azide and tributyl phosphine (1.5 eq) in dry toluene (10 ml) was stirred at 60 °C for 90 min, under an argon atmosphere. The solution was evaporated to dryness and the residue was chromatographed on silica gel, eluting with 2:1 petroleum ether-dichloromethane and then with 1:1 ethyl acetate-petroleum ether.

Starting from **22** (29 mg, 0.066 mmol), a yield of 10 mg (40 %) of **24** was obtained. Starting from **23** (9 mg, 0.023 mmol), a yield of 5 mg (69 %) of **25** was obtained.

Data for **24** (pale yellow oil): IR (NaCl): 1682.2 (CO) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 8.25 (dd, 1H, *J* = 8.0 and 1.1 Hz, H-4); 8.02 (d, 1H, *J* = 8.0 Hz, H-11); 7.74 (td, 1H, *J* = 7.0 and 1.5 Hz, H-2); 7.65 (d, 1H, *J* = 7.0 Hz, H-1); 7.49 (td, 1H, *J* = 7.1 and 1.2 Hz, H-3); 7.25 (m, 2H, H-12,14); 7.13 (t, 1H, *J* = 7.5 Hz, H-13); 6.88 (d, 1H, *J* = 8.0 Hz, H-9a); 6.63 (d, 1H, *J* = 3.0 Hz, H-15); 5.49 (q, 1H, *J* = 7.0 Hz, H-7); 4.95 (dd, 1H, J = 7.9 and 3.0 Hz, H-14b); 2.70 (s, 3H, $N_{10}$-Ac); 1.66 (d, 3H, *J* = 7.0 Hz, $C_7$-$CH_3$). $[\alpha]_D^{25}$ + 73.0 (0.20, $CHCl_3$). MS, *m/z* (%): 398 (16, $M^+$); 356 (100, $M^+$ - Ac); 253 (87, $M^+$ - CO-Ar). HRMS: Calcd. for $C_{23}H_{18}N_4O_3$: 398.1379. Found: 398.1376. Calcd. for $C_{21}H_{16}N_4O_2$: 356.1273. Found: 356.1258.

Data for **25** (pale yellow oil): $^1$H-NMR ($CDCl_3$): δ 8.35 (d, 1H, *J* = 8.0, H-4); 8.20 (d, 1H, *J* = 8.0 Hz, H-11); 8.00 (t, 1H, *J* = 7.0 Hz, H-2); 7.83 (s, 1H, H-15); 7.75 (m, 2H, H-1,3); 7.45 (m, 3H, H-12,13,14); 5.34 (q, 1H, *J* = 7.0 Hz, H-7); 2.35 (s, 3H, $N_{10}$-Ac); 1.65 (d, 3H, *J* = 7.0 Hz, $C_7$-$CH_3$). MS, *m/z* (%): 396 (8, $M^+$); 354 (48, $M^+$ - Ac). Anal. Calcd. for $C_{23}H_{16}N_4O_3$: C, 69.70; H, 4.04; N, 14.14. Found: C, 69.57; H, 3.98; N, 13.97.

### *3.9. Reaction of compound 26 with NBS/AIBN.*

A solution of compound **26** (84 mg, 0.21 mmol), AIBN (3.45 mg, 0.0021 mmol) and NBS (44.85 mg, 0.252 mmol) in carbon tetrachloride (10 ml) was refluxed in an oil bath at 80 °C for 7 h, under an argon atmosphere. The reaction mixture was cooled, and a precipitate of succinimide was filtered off and washed with carbon tetrachloride (2 x 5 ml). Evaporation of the combined filtrates gave a residue, which was purified by column chromatography on silica gel, eluting with 1.5:1 petroleum ether-ethyl acetate, yielding 13 mg (16 %) of compound **27**, as white crystals, 6 mg (5 %) of the unstable compound **28**, as a pale yellow oil, 18 mg (18 %) of compound **29**, as pale yellow crystals, and 30 mg (36 %) of recovered starting material.

Data for **27**: mp 77-78 °C. IR (NaCl): 1685.4 (CO) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 8.26 (d, 1H, *J* = 6.6 Hz, H-4); 8.06 (d, 1H, *J* = 8.0 Hz, H-11); 7.78 (td, 1H, *J* = 6.9 and 1,5 Hz, H-2); 7.68 (d, 1H, *J* = 7.0 Hz, H-1); 7.50 (t, 1H, *J* =7.0 Hz, H-3); 7.34 (m, 2H, H-12,14); 7.15 (t, 1H, *J* = 7.0 Hz, H-13); 6.79 (d, 1H, *J* = 3.6 Hz, H-15); 6.77 (d, 1H, *J* = 8.1 Hz, H-9a); 5.35 (q, 1H, *J* = 6.9 Hz, H-7); 4.77 (dd, 1H, *J* = 8.0 and 3.7 Hz, H-14b); 2.72 (s, 3H, $N_{10}$-Ac); 1.50 (d, 3H, *J* = 6.9 Hz, $C_7$-$CH_3$). MS, *m/z* (%): 398 (17, $M^+$); 356 (100, $M^+$ - Ac). $[\alpha]_D^{25}$ + 69.0 (0.21, $CHCl_3$). Anal. calcd. for $C_{23}H_{18}N_4O_3$: C, 69.35; H, 4.52; N, 14.07. Found: C, 68.63, H, 4.73; N, 13.93.

Data for **28**: $^1$H-NMR ($CDCl_3$): δ 8.32 (d, 1H, *J* = 6.9 Hz, H-4); 8.20 (d, 1H, *J* = 7.0 Hz, H-11); 7.79 (t, 1H, *J* = 6.9, H-2); 7.73 (d, 1H, *J* = 7.8 Hz, H-1); 7.55 (t, 1H, *J* = 6.9 Hz, H-3); 7.36 (m, 2H, H-12,14); 7.19 (t, 1H, *J* = 7.3, H-13); 6.98 (d, 1H, *J* = 7.7 Hz, H-9a); 5.38 (q, 1H, *J* = 6.9 Hz, H-7); 4.94 (s, 1H, H-15); 4.44 (d, 1H, *J* = 7.7 Hz, H-14b); 2.59 (s, 3H, $N_{10}$-Ac); 1.72 (d, 3H, *J* = 6.9 Hz, $C_7$-$CH_3$). Anal. calcd. for $C_{23}H_{18}Br_2N_4O_3$: C, 49.49; H, 3.25; N, 10.04. Found: C, 49.03, H, 3.46; N, 10.29. These data were obtained obtained immediately after purification of **28**; otherwise, the microanalytical data obtained correspond to those expected for compound **29** (see note 15).

Data for **29**: mp 110-112 °C. IR (NaCl): 1682.6 (CO); 1166.7 (*C*=*C*-Br); 756.0 (=*C*-*Br*) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 8.25 (d, 1H, *J* = 8.2 Hz, H-4); 8.03 (d, 1H, *J* = 8.1 Hz, H-11); 7.78 (m, 2H, H-1,2); 7.71 (d, 1H, *J* = 7.6 Hz, H-14); 7.52 (m, 1H, H-3); 7.35 (t, 1H, *J* = 8.2 Hz, H-12); 7.17 (td, 1H, *J* = 7.5 and 1.0 Hz, H-

13); 6.70 (d, 1H, $J$ = 8.2 Hz, H-9a); 5.33 (q, 1H, $J$ = 6.9 Hz, H-7); 4.80 (d, 1H, $J$ = 8.2 Hz, H-14b); 2.67 (s, 3H, $N_{10}$-Ac); 1.42 (d, 3H, $J$ = 6.9 Hz, $C_7$-$CH_3$). MS, *m/z* (%): 478 (7, $M^+$, $^{81}Br$) and 476 (7, $M^+$, $^{79}Br$); 436 (32, $M^+$ - Ac, $^{81}Br$); 434 (32, $M^+$ - Ac, $^{79}Br$); 397 (12, $M^+$ - Br); 355 (82, $M^+$ - Br - Ac); 254 (83, $M^+$ - Br - 2Ac). $[\alpha]_D^{25}$ - 24.8 (0.13, $CHCl_3$). Anal. calcd. for $C_{23}H_{17}BrN_4O_3$: C, 57.86; H, 3.56; N, 11.74. Found: C, 57.58, H, 3.86; N, 11.77.

*3.10. Reaction of compound **30** with NBS/AIBN.*

A solution of compound **30** (35.8 mg, 0.09 mmol), AIBN (1.5 mg, 0.01 mmol) and NBS (19.1 mg, 0.107 mmol) in carbon tetrachloride (10 ml) was treated as indicated in section 3.1 (reaction time, 4 h). Chromatography on silica gel, eluting with 2:1 petroleum ether-ethyl acetate, yielded 17 mg (34 %) of the unstable compound **31** as a pale yellow oil, 14 mg (33 %) of compound **32** as pale yellow crystals, and 10 mg (28 %) of recovered starting material.

Data for **31**: $^1$H-NMR ($CDCl_3$): δ 8.31 (d, 1H, $J$ = 7.1 Hz, H-4); 8.19 (d, 1H, $J$ = 7.0 Hz, H-11); 7.79 (t, 1H, $J$ = 6.9 Hz, H-2); 7.74 (d, 1H, $J$ = 7.7 Hz, H-1); 7.55 (t, 1H, $J$ = 6.9 Hz, H-3); 7.36 (m, 2H, H-12,14); 7.19 (t, 1H, $J$ = 7.4 Hz, H-13); 7.00 (d, 1H, $J$ = 7.8 Hz, H-9a); 5.40 (q, 1H, $J$ = 6.9 Hz, H-7); 4.95 (s, 1H, H-15); 4.45 (d, 1H, $J$ = 7.6 Hz, H-14b); 2.60 (s, 3H, $N_{10}$-Ac); 1.72 (d, 3H, $J$ = 6.9 Hz, $C_7$-$CH_3$).

Data for **32**: mp, 110-112 °C. IR (NaCl): 1682.4 (CO); 1168.9 (*C*=*C*-Br); 757.0 (=*C*-*Br*) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 8.26 (d, 1H, $J$ = 8.2 Hz, H-4); 8.04 (d, 1H, $J$ = 8.0 Hz, H-11); 7.79 (m, 2H, H-1,2); 7.71 (d, 1H, $J$ = 7.5 Hz, H-14); 7.52 (m, 1H, H-3); 7.36 (t, 1H, $J$ = 8.1 Hz, H-12); 7.17 (t, 1H, $J$ = 7.5, H-13); 6.70 (d, 1H, $J$ = 8.2 Hz, H-9a); 5.34 (q, 1H, $J$ = 6.9 Hz, H-7); 4.81 (d, 1H, $J$ = 8.2 Hz, H-14b); 2.67 (s, 3H, $N_{10}$-Ac); 1.43 (d, 3H, $J$ = 6.9 Hz, $C_7$-$CH_3$). $^{13}$C-NMR ($CDCl_3$): δ 170.43 (*C*O-$CH_3$); 163.24 (C-8); 159.42 (C-5); 146.51 (C-4a); 141.19 (C-10a); 139.68 (C-15b); 136.44 (C-15a); 134.38 (C-2); 129.28 (C-12); 128.90 (C-14a); 127.89 (C-1); 126.75 (C-3); 126.62 (C-4); 125.02 (C-13); 123.59 (C-14); 120.68 (C-16a); 118.98 (C-11); 109.28 (C-15); 77.96 (C-9a); 55.02 (C-14b); 53.78 (C-7); 23.99 (CO-*C*$H_3$); 19.97 ($C_7$-$CH_3$). MS, *m/z* (%): 436 (32, $M^+$ - Ac, $^{81}Br$); 434 (33, $M^+$ - Ac, $^{79}Br$); 397 (26, $M^+$ - Br); 355 (100, $M^+$ - Br - Ac). $[\alpha]_D^{25}$ + 25.0 (0.12, $CHCl_3$). Anal. calcd. for $C_{23}H_{17}BrN_4O_3$: C, 57.86; H, 3.56; N, 11.74. Found: C, 57.68, H, 3.85; N, 11.50.

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## 5. References and notes

1 a) Biological activity: Karwowski, J. P.; Jackson, M.; Rasmussen, R. D.; Humphrey, P. E.; Poddig, J. B.; Kohl, W. L.; Scherr, M. H.; Kadam, S.; McAlpine, J. B. *J. Antibiotics* **1993**, *46*, 374. b) Isolation and structure: Hochlowski, J.E.; Mullally, M. M.; Spanton, S. G.; Whittern, D. N.; Hill, P.; McAlpine, J. B. *J.*

*Antibiotics* **1993**, *46*, 380. c) Total synthesis: Marsden, S. P.; Depew, K. M.; Danishefsky, S. *J. Am. Chem. Soc.* **1994**, *116*, 1143.

2 Kane, S. E. *Adv. Drug Res.* **1996**, *28*, 181.

3 a) Hodge, R. P.; Harris, C. M.; Harris, T. M. *J. Nat. Prod.* **1988**, 51, 66. b) Arai, K.; Kimura, K.; Mushiroda, T.; Yamamoto, Y. *Chem. Pharm. Bull.* **1989**, *37*, 2937.

4 a) Scott, P. M.; Marie-Annick, M.; Polonsky, J. *Experientia* **1976**, *32*, 140. b) Chen, W.-C.; Joullié, M. M., *Tetrahedron Lett.* **1998**, *39*, 8401.

5 a) Caballero, E.; Avendaño, C.; Menéndez, J. C. *Tetrahedron: Asymmetry* **1998**, *9*, 967. b) Caballero, E.; Avendaño, C.; Menéndez, J. C. *Tetrahedron: Asymmetry* **1998**, *9*, 3025.

6 See also: Madrigal, A.; Grande, M.; Avendaño, C. *J. Org. Chem.* **1998**, *63*, 2724, and references therein.

7 Bruncko, M.; Crich, D.; Samy, R. *J. Org. Chem.* **1994**, *59*, 5543.

8 MM2 calculations give a value of 90.4° for the H-C(10b)-C(11)-H dihedral angle.

9 Review on the use of free-radical reactions in the synthesis of aminoacids and their derivatives: Easton, C. J. *Chem. Rev.* **1997**, *97*, 53.

10 In the case of the reaction described by Crich, steric hindrance of the tryptophan stereocenter by the side chains of the two neighbouring carboxylate groups probably prevented its bromination. This hindrance is not present in our more rigid starting materials.

11 Easton, C. J.; Hay, M. P.; Love, S. G. *J. Chem. Soc., Perkin Trans. 1* **1988**, 265.

12 a) Yoshimura, J.; Nakamura, H.; Matsunari, K. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 605. b) Yoshimura, J.; Sugiyama, Y.; Nakamura, H. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2850.

13 See, for instance: March, J., Advanced Organic Chemistry, 4th. edition, pp. 681-682. John Wiley and Sons, 1992.

14 For a precedent of this type of epimerization on a similar substrate, see reference 5a.

15 In a related observation, mass spectra of compound **14** and the related dibromo derivatives **28** and **31** were identical to those of the corresponding dehydrobromination derivatives (compounds **15**, **29** and **32**, respectively).