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Study on medium ring heterocycles: synthesis and structure of novel condensed pyrazolo[1,4]diazocinones including single enantiomers

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ABSTRACT

By means of a base-catalysed ring enlargement of triazapentalenoindenes resulting from diasteroselective anhydride-induced ring transformation of chiral aminoalcohol-derived zwitterionic 2,3-dihydroimidazo[2,1-*a*]phthalazinium-olates, a series of pyrazolo[1,5-*d*][1,4]diazocin-7(6*H*)-ones with central and conformational chirality were obtained in enantiomerically pure form. The possible reasons of the characteristic substrate- and reagent-dependency observed for the diasteroselective ring transformations of the zwitterions were interpreted in terms of the relative energetics of the crucial alternative imidazolinium intermediates disclosed by B3LYP/6-31G(d,p) calculations. The trans-annular opening of three epimeric pairs of triazapentalenoindanones afforded identical pyrazolodiazonine products. This finding suggests that the primarily formed diastereomers, having different asymmetric conformations but the same element of central chirality, undergo ring inversions in one- and two steps, respectively, involved in pathways previously established for the facile racemisation of pyrazolodiazocines with conformational chirality and hydrogen- or methyl-substituent at C1-position. The ring enlargement of triazapentalenoindanones resulted from butyric anhydride-mediated ring transformation of zwitterions with symmetrical substitution pattern afforded highly rigid 1-ethylpyrazolodiazocines in racemic form potentially separable without thermal racemisation. The constitution, conformation and relative configuration of the novel compounds were determined by ^{1}H-, ^{13}C- and ^{15}N-NMR methods including 2D-HSQC, 2D-HMBC and DNOE measurements and the structure of a pyrazolodiazocine was supported by single crystal X-ray diffraction.

1. Introduction

Medium ring heterocycles are often present in biologically active natural products and in a wide range of drug candidates. Their synthesis by conventional direct ring closure methods may often be difficult unless certain conformational restraints are present in the acyclic precursor.[1] Alternative synthetic approaches of structures containing medium-size ring systems of potential biological interest are based on diverse ring transformation reactions.[2–10] Different benzodiazocines- and benzodiazonines result from the oxidative ring expansion of polycyclic fused compounds often containing indole unit[2–4] or intramolecular transacylation of 1-[2-(ω-aminoalkyl)-phenyl]-azetidin-2-ones.[5] On the other hand, in certain cases the transitionally formed medium-size rings cannot be isolated as they immediately undergo trans-annular ring contraction to give smaller condensed rings. For instance, alternative trans-annular condensations of 3,4,5,6-tetrahydro-1*H*-benzo[*e*][1,4]diazonine-2,7-diones transitionally formed by the oxidative ring fission of 1,2,3,4-tetrahydrocarbolines led to the formation of 1,2,3,4-tetrahydropyrrolo[3,4-*b*]quinolinones or[6a] 1,2,3,4-tetrahydropyrrolo [2,3-*c*]quinolinones.[6b] Another characteristic example is the ring isomerisation of pyridazino[1,2-*c*][1,3,4]thiadiazinones into thiazolo[3,4-*a*][1,3]diazepinones involving the cleavage of the N–N bond followed by diastereoselective trans-annular recyclisation of the intermediate 1,3,8-thiadiazecinones.[7] The biological activity associated with the receptor-binding properties of medium-size heterocycles depends not only on pharmacophoric grouping,[8] but also on the conformation.[9] By means of the combined use of NMR, X-ray analysis and molecular modelling of some benzodiazepine and benzotriazepine derivatives, a nonplanar rapidly interconverting (on the NMR time scale) boat shape conformation were established for the seven-membered ring in agreement with the results of X-ray analyses.[8–14] Experimental and theoretical conformational studies of the more flexible benzodiazocine and benzodiazonines have also been reported,[4,15–19] but there are a relatively low number of examples of synthesis and structural analysis of their polycyclic hetero condensed derivatives.[20–26]

In our previous paper we reported on the synthesis and ring inversion of the pyrazolo[1,5-*e*]benzo[*g*][1,5]diazonin-8(7*H*)-ones **1a**–**c** and pyrazolo[1,5-*d*]benzo[*f*][1,4]diazocin-7(6*H*)-ones **2a**,**b** (Fig. 1). These medium-size heterocycles with conformational

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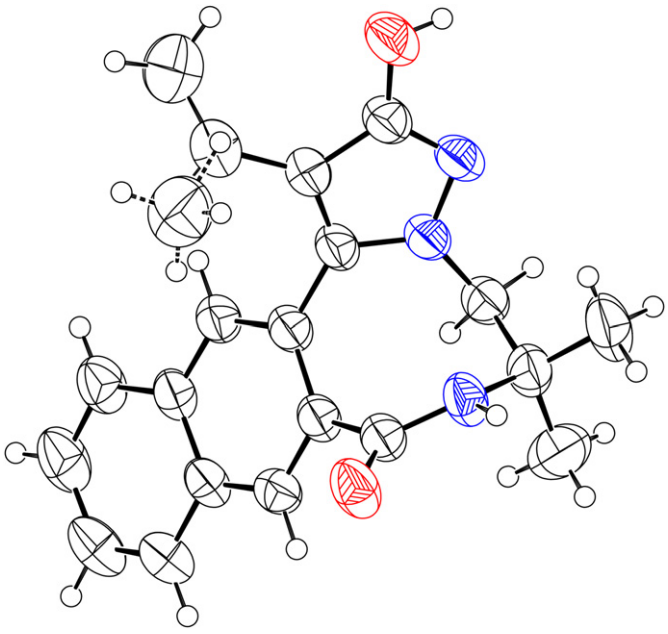


Fig. 1. A 50% displacement representation of a single **7c** molecule from the crystal structure. Broken lines indicate minor disorder methyl terminus of the ethyl group (plotted by the aid of PLATON[32]).

chirality were prepared in racemic form and their substituent-dependent ring inversion associated with the change in chirality was studied by DNMR and DFT calculations.[27] It has been established that the methyl-or the phenyl-group attached to the C1 position affords complete rigidity to the pyrazolodiazonine skeleton (**1b**,**c**), while the methyl-substituent in the same position of **2b** has no significant effect on the conformational stability of the pyrazolodiazocine ring system.[27]

As a continuation of our ongoing research on medium-size ring systems we envisaged the synthesis of further representatives of pyrazolodiazocines having potential interest in CNS-oriented assays, including 2-aminoalcohol-based derivatives in an enantiopure form. We also expected that the replacement of the methyl group for an ethyl substituent in position 1 would result in a significant decrease in the conformational flexibility of this ring system (Scheme 1).

2. Results and discussion

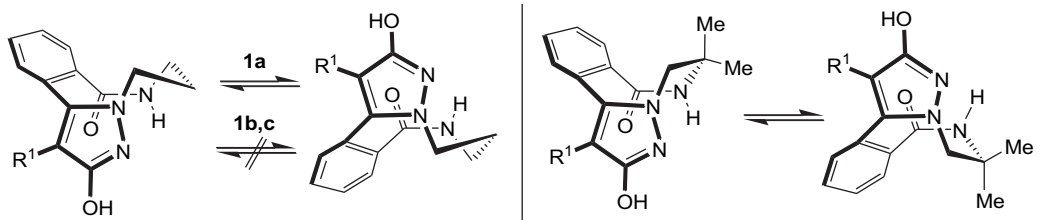
2.1. Preparation and conformational flexibility of the novel diazocines without central chirality

First we assessed the feasibility of incorporating butyric anhydride in the tetra- and pentacyclic triazapentalenoindenones **5c** and **6c** (Scheme 2), the potential precursors of 1-ethyl-substituted pyrazolodiazoninoses **2c** and **7c**, respectively. Upon heating dimethyl-substituted zwitterions **3**[28] and **4** with this reagent at reflux the expected ring-transformations occurred producing **5c** and **6c** in mediocre yields, as these reactions were accompanied by the formation of substantial amounts of tarry materials. After a shorter reaction with hydrazine hydrate in ethanol at reflux (method A), **5c** and **6c** underwent N3-deacylation associated with trans-annular ring opening leading to **2c** and **7c**, respectively, in low yields. By the use of 10% $NaHCO_3$ (reflux) as reagent (method B) higher yields could be achieved (Scheme 2). The relatively low yields obtained by method A suggest that the efficiency of hydrazine-mediated C1-deprotonation seems to be more susceptible to the steric demand of R^1-substituent than that of the reactions with hydroxide ions. This view is supported by the higher yields of **7a**,**b** obtained by the hydrazine-mediated ring enlargements of pentacycles **6a**,**b**, which were resulted from the reactions of **4** with acetic- and propionic anhydride, respectively (Scheme 2).

In keeping with our expectations the ^1H NMR analysis of the novel pyrazolodiazocines carried out in DMSO-d_6 solution at different temperatures disclosed that R^1=ethyl group renders complete rigidity of the eight-membered ring as reflected by the fact that even no line broadening could be detected when the solutions of **2c** and **7c** were heated up to 390 K (for technical precaution the temperature was not raised above this temperature.) This resistance to undergo racemisation can obviously be due to a severe repulsive interaction of the proximal H11(in **2c**)/H13(in **7c**) proton and the intensively rotating methyl group inside the ethyl substituent, which prevents the crucial flip of the pyrazole ring on the pathway revealed for the inversion of the pyrazolodiazocine scaffold.[27] Accordingly, by means of ^1H NMR measurements 368 K and 376 K were measured as coalescence temperatures for the ring inversions of **7a** and **7b**, respectively, exhibiting definite conformational and consequently configurational flexibility.

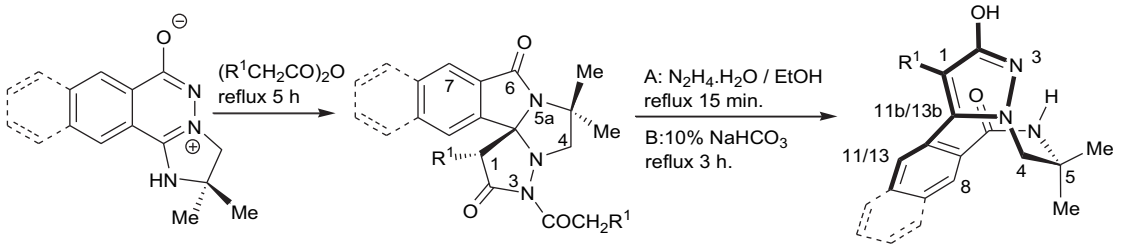
2.2. Preparation of single enantiomers of novel diazocines with central and conformational chirality

Making use of this facile reaction sequence involving anhydride-induced ring transformation and deacylation associated with ring enlargement we undertook the synthesis of benzo- and naphtho-condensed pyrazolodiazocines with central and conformational chirality in enantiopure form (Scheme 3). First, valinol-based zwitterion **8**[28] was treated with anhydrides at reflux to get chiral tetracycles **12a**,**b**[28] and **12c**. Using acetic- and propionic anhydrides zwitterions **9** and **10** were converted into chiral tetra- and pentacyclic compounds **13a**,**b**, **14a** and **15a** with R^2 group in *endo* position as well as *exo*-substituted diastereomers **13a*** and **15a*** considered as potential precursors of further optically active pyrazolodiazocines containing the elements of central and conformational chirality. The ring enlargement of the tetra- and pentacyclic intermediates was first attempted by hydrazine in ethanol at reflux



The signs (P) and (M) are used arbitrarily for these compounds.

Scheme 1.



3 benzo
4 naphtho

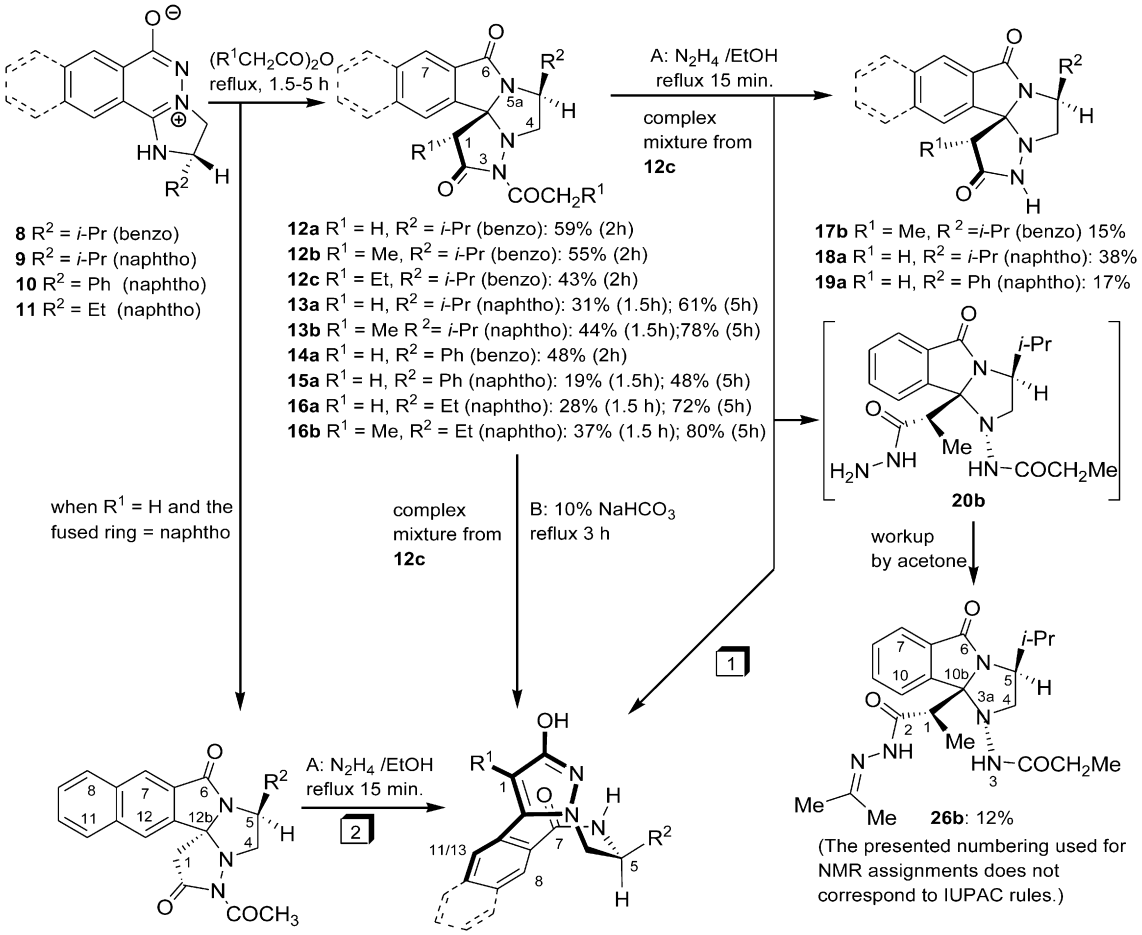
5c (benzo): 49%
6a (naphtho): 92%
6b(naphtho): 65%
6c (naphtho): 63%

a: R^1 = H
b: R^1 = Me
c: R^1 = Et

2c (benzo): 22% (A); 53% (B)
7a (naphtho): 48% (A); 58% (B)
7b (naphtho): 42% (A); 52% (B)
7c (naphtho): 20% (A); 49% (B)

For compounds **2c**, **5c**, **6a-c** and **7a-c** the relative configurations are represented on this Scheme.

Scheme 2.



8 R^2 = *i*-Pr (benzo)
9 R^2 = *i*-Pr (naphtho)
10 R^2 = Ph (naphtho)
11 R^2 = Et (naphtho)

12a R^1 = H, R^2 = *i*-Pr (benzo): 59% (2h)
12b R^1 = Me, R^2 = *i*-Pr (benzo): 55% (2h)
12c R^1 = Et, R^2 = *i*-Pr (benzo): 43% (2h)
13a R^1 = H, R^2 = *i*-Pr (naphtho): 31% (1.5h); 61% (5h)
13b R^1 = Me R^2= *i*-Pr (naphtho): 44% (1.5h);78% (5h)
14a R^1 = H, R^2 = Ph (benzo): 48% (2h)
15a R^1 = H, R^2 = Ph (naphtho): 19% (1.5h); 48% (5h)
16a R^1 = H, R^2 = Et (naphtho): 28% (1.5 h); 72% (5h)
16b R^1 = Me, R^2 = Et (naphtho): 37% (1.5 h); 80% (5h)

17b R^1 = Me, R^2 =*i*-Pr (benzo) 15%
18a R^1 = H, R^2 = *i*-Pr (naphtho): 38%
19a R^1 = H, R^2 = Ph (naphtho): 17%

13a* R^2 = *i*-Pr: 28% (1.5h)
15a* R^2 = Ph: 23% (1.5h)
16a* R^2 = Et: 36% (1.5h)

11, **16a**,**b**, **16a*** and **25a**,**b** (R^2 = Et) are also represented as single enatiomers.

21a R^1 = H, R^2 = *i*-Pr (benzo): 37% (A/1); 55% (B)
21b R^1 = Me, R^2 = *i*-Pr (benzo): 20% (A/1); 49% (B)
22a R^1 = H, R^2 = *i*-Pr (naphtho): 38% (A/1); 50% (B); 86% (A/2)
22b R^1 = Me, R^2 = *i*-Pr (naphtho): 31% (A/1); 49% (B)
23a R^1 = H, R^2 = Ph (benzo): 28% (A/1); 52% (B)
24a R^1 = H, R^2 = Ph (naphtho): 17% (A/1); 32% (B); 81% (A/2)
25a R^1 = H, R^2 = Et (naphtho): 62% (A/1); 78% (A/2)
25b R^1 = Me, R^2 = Et (naphtho): 58% (A/1)

A/1 and A/2 refer to the yields of **22a**, **24a** and **25a** obtained from the hydrazine-mediated reactions of *endo*- and *exo*- diastereomers, respectively.

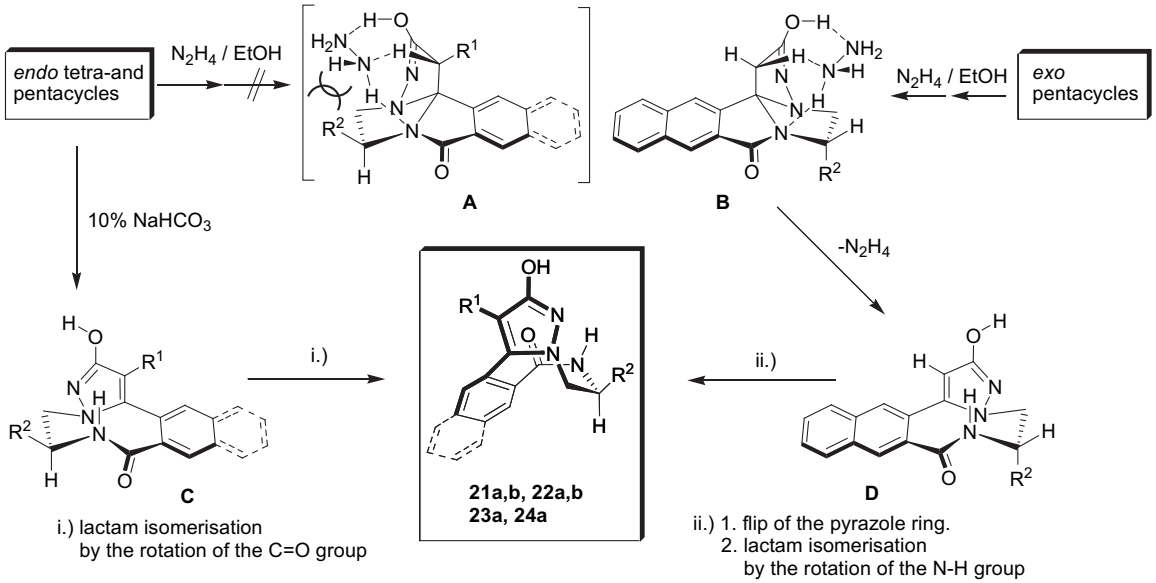
Scheme 3.

(method A), but the reactions of most *endo* diastereomers resulted in pyrazolodiazocines contaminated by a number of undefined side-products significantly decreasing the isolated yields (17–37%: Scheme 3). Since acetone was employed for the workup for the reaction mixtures obtained by method A, besides **21b** (20%) and a deacylated product (**17b**: 15%) hydrazone **26b** could also be separated in low yield (12%) after the reaction of **12b**. Imidazo[1,2-*a*] isoindolone **20b**, the precursor of **26b**, was formed by the hydrazine-mediated fission of the pyrazole ring giving information on the unwanted side reactions involving other amide/imide type bonds present in the intermediates. The limited success of the attempted reactions conducted under the conditions of method A prompted us to resort to the application of 10% aqueous $NaHCO_3$ (method B), which proved to be successful to effect ring enlargement of the optically active triazapentalenoindanones of types **21**–**24** in mediocre yields (Scheme 3), but the reaction of **12c** gave again a highly complex, practically unseparable mixture of products. The racemic mixtures of pentacycles **16a**,**b** with slightly less demanding R^2=ethyl group were also prepared by anhydride-induced rearrangement reactions of zwitterion **11**. Contrary to the substrates with bulkier R^2 substituents these models readily underwent hydrazine-mediated deacylation by method A associated with trans-annular ring opening affording **25a**,**b** in quite good yields (62% and 58%), and under the same conditions pentacycles **13a***, **15a*** and **16a*** with *exo*-oriented R^2 group got also converted into the corresponding pyrazolo-naphthodiazonines (**22a**, **24a** and **25a**) in 78–86% yields.

The remarkable substrate-dependence observed in the reactivity of diastereomer pairs **13a**/**13a***, **15a**/**15a*** and **16a**/**16a*** towards hydrazine suggests that these are the bulkier R^2 groups situated in *endo* position that may prevent the ring enlargement. This experience can be explained by comparing the structures of the assumed complexes types **A** and **B** composed of hydrazine and the anchoring iminohydrine tautomer resulted from the deacetylation of the *endo*- and *exo*-diastereomers, respectively (Scheme 4). It seems reasonable that too bulky R^2-groups (*i*-Pr, Ph) may prevent the formation of crowded complexes type **A**, the prerequisite of the actual ring opening step. In these cases the ring fission leading to complexes **C** can be effected by the sterically less demanding hydroxide ion present in the 10% $NaHCO_3$ solution proved to be successful reagent for most of our studied transformations affording pyrazolodiazocines with central- and conformational chirality. In the complexes type **B** with smaller degree of steric crowdance the hydrazine molecule anchored by hydrogen bond from the hydroxypyrazoline moiety may promote the ring enlargement simultaneously operating as base- and acid catalyst to result in the formation of intermediates type **D**.

The trans-annular ring enlargement of both *endo*- and *exo*-diastereomers gives identical pyrazolo-naphthodiazocine products as the consequence of a single lactame-isomerisation by the rotation of the C=O group in the intermediates type **C**, and the flip of the pyrazole ring followed by lactame-isomerisation taking place by the rotation of the N–H group in the diastereomeric intermediates type **D** (Scheme 4). It is to be noted here that besides this proposed mechanism involving hydrogen-bonded hydrazine-complexes of deacylated triazapentalenoindanones other competitive reaction pathways with simple proton transfers contributing to the formation of pyrazolodiazocines must also be taken into account for the overall reactions affording isolable amount of the medium ring-size products.

An interesting feature of the anhydride-induced ring transformations of zwitterions is the characteristic substrate-, reagent- and time dependent formation of *endo*- and *exo* diastereomers of the tetra- and pentacyclic products of types **12**–**16** (Scheme 4). Besides the corresponding *endo*-diastereomers (18–31%) somewhat higher yields (23–36%) of *exo*-diastereomers (**13a***, **15a*** and **16a***) were obtained when naphtho-condensed zwitterions were treated with refluxing acetic anhydride employing shorter reaction time (1.5 h). Prolonged treatment (5 h) with the same reagent afforded *endo* diastereomers (**13a**, **15a** and **16a**) as only isolable products referring to their possible formation under thermodynamic control from the corresponding *exo*-isomer, the primarily formed 'kinetic products'. Since the preparative outcome of these experiments apparently contradicted the general expectations, the relative free energy values of the optimized structures of representative diastereomeric model pairs with R^2=*i*-Pr substituent (**12a***/**12a**, **12b***/**12b**, **13a***/**13a** and **13b***/**13b**) were calculated with the dependence of the R^1 group and the condensed aromatic ring. The optimized structures and the thermodynamic parameters were obtained by DFT calculations[29] carried out at B3LYP/6-31G(d,p) level of theory.[30,31] In each case studied, the result was in agreement with the experiments showing a somewhat higher thermodynamic stability of the *endo* isomer and that the bulkier R^1=Me group slightly facilitates the formation of *endo* products [ΔG



Scheme 4.

(*exo*–*endo*) calculated for 413 K and 440 K, respectively, representing the boiling points of the reagent anhydrides, which are approximated to be identical with the reaction temperatures: +2.65 kcal/mol (**12a***/**12a**); +3.60 kcal/mol (**12b***/**12b**); +2.70 kcal/mol (**13a***/**13a**); +3.49 kcal/mol (**13b***/**13b**), Table 1]. It is, however, an important point that only the acetic anhydride-mediated reactions of naphtho-condensed zwitterions **9**–**11** afforded *exo* diastereomers in isolable amounts. In order to disclose the reason for this substrate- and reagent-dependent diastereoselectivity first we composed reaction pathways connecting the precursor zwitterions with all the possible tetra- and pentacyclic products (Scheme 5), and undertook again comparative B3LYP/6-31G(d,p) analysis of the key intermediates of types **G** and **F** resulted from the protonation of imidazoline ring (Q=H) and involved in the conversions leading to our selected representative model pairs with R^2=*i*-Pr group (**12a***/**12a**, **12b***/**12b**, **13a***/**13a** and **13b***/**13b**, cf. Table 1). The pathway accounting for the formation of *endo* products comprises the reagent-mediated fission of the *N*-acylated pyridazinone ring (**E**→**F**) and the crucial diastereoselective formation of the C–C bond in the resulted imidazolium salt finally followed by the closure of the pyrrolidone ring effected by the residual mixed anhydride moiety. Since the cationic intermediates (type **F**) were supposed to be stabilized by a non-bonding C···O interaction from the trans position relative to the bulky R^2 group allowing the enol-attack from this side, we have previously proposed this mechanism for the conversion of a series of benzo-condensed zwitterions affording selectively *endo*-substituted tetracycles (e.g. **12a** and **14a**).[28] On the other hand, the ring closure of the mixed anhydride intermediates **F** may also lead to cyclic imidazolium salts (**G**) of which alternative cylisations are capable of affording either diastereomeric product. The optimized structures of intermediate cations (**G** and **F**) and their thermodynamic parameters were obtained by B3LYP/6-31G (d,p) (Table 1). The presence of the aforementioned non-bonding C···O interaction in the intermediates type **F** is evidenced by the distance between the atoms involved (Table 1). In keeping with the general expectations the relative free energy values calculated for the reaction temperatures (boiling points of the employed anhydrides: 413 K and 440 K, respectively) indicate that the fused naphthalene ring facilitates cyclisations type **F**→**G** rather than does the benzene ring of less pronounced π-electron donating character, opening the route to the *exo*-products. However, since cyclisations of the type **F**→**G** are accompanied by a characteristic substituent-dependent decrease in entropy (Table 1), R^1=Me suppresses this step indirectly preventing the formation of *exo*-diastereomers, particularly at higher temperatures.

2.3. Structure determination

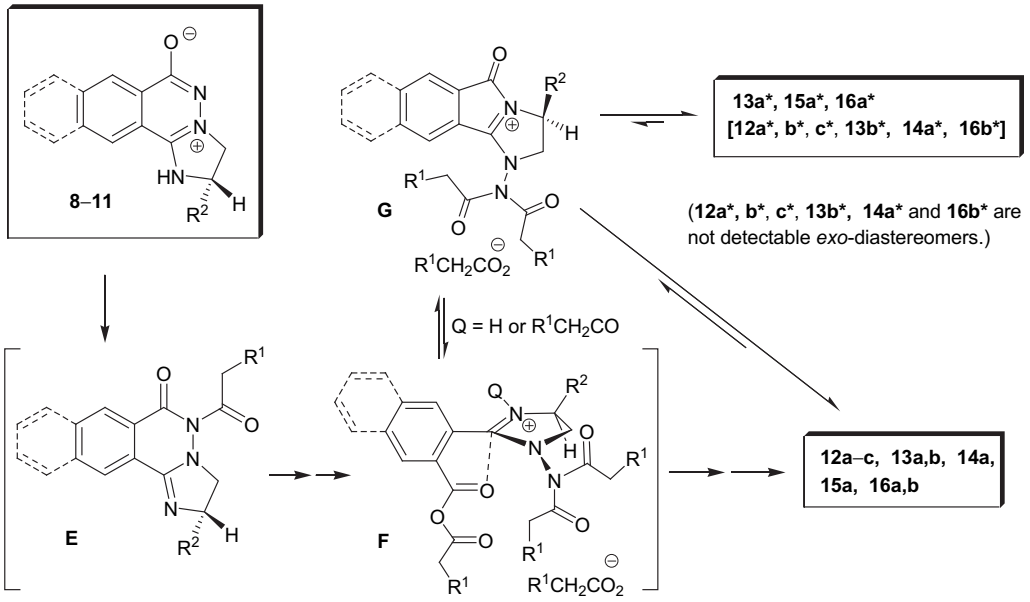
The IR- ^{1}H- ^{13}C- and ^{15}N-NMR data of the novel triazapentalenoindanones and pyrazolodiazocines (see Experimental section) are consistent with their structures and similar to those reported for analogous compounds,[27,28] however, the following remarks are necessary.

The structure of pentacycles **13a***, **15a*** and **16a*** was unambiguously evidenced by mutual NOEs (2–4%) due to interactions of $H1_{endo}$ with $H4_{endo}$ and H5, respectively. Due to the anisotropic effect of the proximal 6-oxo group in **13a*** and **16a*** the CH- or CH_2-signals of R^2 group are considerably downfield shifted (by 0.7–1.2 ppm) relative to those of **13a** and **16a**, respectively. In the *endo*-diastereomers types **12**–**16** enhanced NOEs (4–8%) were detected between $H1_{endo}$ and the protons of R^2 group. Analogously, in **5c**, **6b**,**c**, **12b**,**c**, **13b**, **16b** and **17b** the *exo* position of R^1=Me or Et

Table 1
Non-bonding C···O distance in representative intermediates type **F** (Q=H) and thermodynamic parameters of their ring closure affording cyclic imidazolinium cations type **G** calculated by B3LYP/6-31G(d,p) method

R^1; condensed ring	d(C···O) in **F** [Å]	Δ*G*(*exo*–*endo*) at $T_{reaction}$[a] [kcal/mol]	Δ*S*(**G**–**F**) [cal/mol K]	Δ*G*(**G**–**F**) at $T_{reaction}$[a] [kcal/mol]
H; benzo	2.613	+2.65	−27.68	+0.16
H; naphtho	2.607	+3.60	−27.86	**−1.96**
Me; benzo	2.607	+2.70	−34.92	+1.72
Me; naphtho	2.608	+3.49	−35.22	−0.30

[a] Boiling point of acetic- and propionic anhydrides (413 K and 440 K, respectively).



Scheme 5.

substituent was also evidenced by NOEs of similar intensity (5–9%) detected between H1$_{endo}$ and the protons of R^2 group.

The constitution of imidazo[1,2-*a*]indanone **26b** was supported by the C1 and C10b signals at 43.0 ppm and 97.2 ppm, respectively, and by the presence of five nitrogen atoms of which positions could unequivocally be located via the coupling patterns discernible in the ^{1}H–^{15}N-HMBC spectrum: e.g. the skeletal N3a atom can be identified from the cross peaks with H1-, 3NH-, H4$_{exo}$-, H4$_{endo}$- and H5$_{eq}$ signals (*endo* designates cis position relative to *i*-Pr group). Accordingly, the ^{1}H–^{13}C-HMBC spectrum reveals correlations between the aforementioned protons and C10b, which gives further cross peaks with H10 and the protons of the 1-CH$_3$ group. The relative trans orientation of C1 and N3 atoms is reflected by the mutual NOEs (4–9%) measured between H1 and the CH proton of *i*-Pr group and resulted from the interaction involving 3NH- and H4$_{exo}$ protons.

The structures of pyrazolodiazocines **2c**, **7a**–**c**, **21a**,**b**, **22a**,**b**, **23a**, **24a** and **25a**,**b** containing aromatic hydroxypyrazole ring and '*Z*'-lactam moiety are consistent with the related ^{1}H-, ^{13}C- and ^{15}N-NMR data (see Experimental section) and supported by the following NOE experiments. Considerable NOEs (7–10%) were measured between the lactam NH and the protons of the *exo*-positioned R^2 group pointing to their relative cis position on the eight-membered ring. As an additional evidence for the boat conformation of the eight-membered ring mutual NOEs (4–6%) were detected between the protons of the *endo*-positioned methyl group and the H8 proton of the condensed aromatic ring (**2c**, **7a**–**c**). Smaller, but significant NOEs (2–3%) could be obtained between the *endo*-positioned H5 proton and the H8 proton on the condensed aromatic ring in **21a**,**b**, **22a**,**b**, **23a**, **24a** and **25a**,**b**. Providing further evidence for the boat conformation of the eight-membered ring present in these compounds diagnostic NOEs were measured between the proton pairs H4$_{endo}$–H5 (12–14%), H4$_{endo}$–H11 (benzo-fused)/H13 (naphtho-fused) (3–5%) and H4$_{exo}$–NH (4–6%). The solid state structure of **7c** was determined by single crystal X-ray analysis (summary of data: CCDC 801193).

2.4. Crystal structure description of pyrazolodiazocine 7c

Pyrazolodiazocinone **7c** was also studied by single crystal X-ray analysis. Its crystal structure, in spite of the nice looking crystals poses some irregularities, interesting organization and stoichiometry features. First of these is the involvement of a molecule of acetonitrile crystallization solvent included in an apparently centrosymmetric structure with half occupancy in the asymmetric unit. Along with two **7c** molecules in the asymmetric unit this then yields to the overall 4/1 stoichiometry of the crystal. The **7c** molecular structure alone (Fig. 1) shows the disorder of the ethyl group at C1. Peculiar ethyl disorder and the half occupancy might raise the idea of reducing the space group symmetry to the chiral *P*1 space group. However this hypothesis could not be verified convincingly.

Two kinds of functions of molecules **7c** are seen in the crystal (Fig. 2). Both types represent dimer associations of **7c** molecules, but these types involve differing ring involvements. The type 1 dimer placement for the molecules is at around in the cell linking opposite facing diazocine NH···O=C functions across the symmetry center at 1/2, 1/2, 1/2. The type 2 dimers, placed at the face centers at *0*, *1/2*, *0* and through the 5-ring N3 atom as the acceptor and the O1 HB donor function, serve for structure propagation along the crystallographic '*a*' axis. The connection between the two dimer types as well as the structure propagation occurs via the O1H···O2 hydrogen bridges along the *c* direction, together with a slightly longer but geometrically regular N6···N3 hydrogen bridge contact. The role of the solvent appears to be filling otherwise empty space in the crystal and probably only contributing to the crystal stabilization through non-specific weaker dispersion forces.

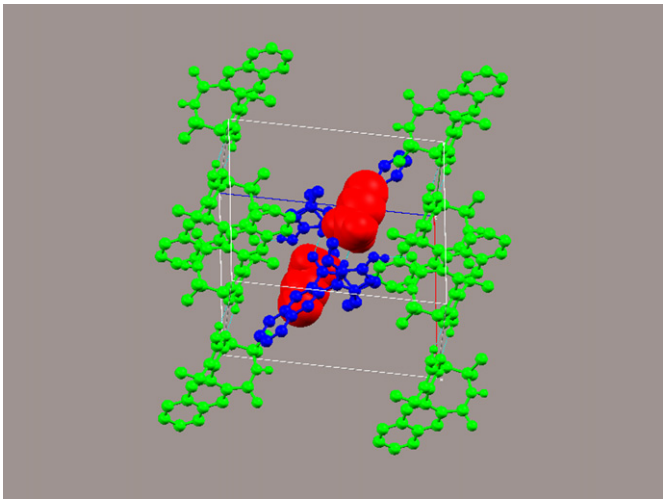


Fig. 2. Different coloured *type 1* (blue) and *type 2* (light green, see text) residues with their H-bridge contacts in broken lines, space filling representation of acetonitrile solvent is also indicated in red (packing excerpt by the aid of mercury[33]).

3. Conclusion

Anhydride-induced diasteroselective ring transformation reactions of condensed zwitterionic imidazopyridazinium olates followed by base-catalysed trans-annular ring enlargement were utilized for the convenient synthesis of a series of novel optically active pyrazolodiazocines with the elements of central- and conformational chirality of potential interest in biological test. Taking into account the structure–reactivity relationships established experimentally and partly interpreted by high-level DFT calculations, the expedient procedures employed in the subsequent steps may open up a way to a number of further representatives of this medium-size ring system. It is a remarkable advantage of the synthetic routes described in this contribution that the absolute configuration of the target compounds can be determined by the configuration of a particular enantiomer of the chiral aminoalcohol incorporated in the easily available precursors. It was also established that, due to subsequent ring inversion steps, the ring enlargement reactions of both *endo*- and *exo* triazapentalenoindanones lead to identical pyrazolodiazocines with conformational- and central chirality. From the perspective of enantiomer-separation it may be of importance that as ethyl group was found to be the sterically least demanding substituent in position 1, which is capable of preventing the thermal racemisation of pyrazolodiazocinones with symmetrical substitution pattern even at elevated temperatures. Accordingly, experiments to achieve optical resolution of **2c** and **7c** are in progress.

4. Experimental section

4.1. General

Melting points (uncorrected) were determined with a Boethius microstage and are uncorrected. Flash silica gel column chromatography was carried out on Merck Kieselgel 60 (230–400 mesh). The IR spectra were run in KBr disks on a Bruker IFS-55 FT-spectrometer controlled by Opus 3.0 software. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 or CDCl$_3$ solution in 5 mm tubes at rt, on a Bruker DRX-500 spectrometer at 500.13 (^{1}H) 125.76 (^{13}C) and 50.12 (^{15}N) MHz, with the deuterium signal of the solvent as the lock and TMS as the internal standard (for ^{1}H and ^{13}C NMR) and NH$_{3liq}$ as external reference (^{15}N NMR). The ^{15}N NMR chemical shifts were obtained and assigned from the 2D ^{1}H–^{15}N HMBC spectra. The standard Bruker microprogram NOEMULT to generate

NOE and to get DIFFNOE spectra was used with a selective pre-irradiation time. DEPT spectra were run in a standard manner, using only a Θ=135° pulse to separate the CH/CH_3 and CH_2 lines phased 'up' and 'down', respectively. The 2D-COSY-, HMQC- and HMBC spectra were obtained by using the standard Bruker pulse programs. Optical rotations were measured with a Zeiss Polamat A polarimeter. All calculations were carried out with the Gaussian 03 suite of programs.[34] On request the optimized structures are available from the authors.

4.2. Crystal structure determination of 7c

4.2.1. Crystal growth. Regular prism shaped transparent crystals of **7c** were grown from a mixture of acetonitrile/ethanol (1/1) solution by slow solvent evaporation. A crystal selected from the batch in equilibrium with its mother liquor was used for the X-ray data collection.

4.2.2. Crystal structure determination. A selected single crystal (0.2×0.3×0.5 mm) of **7c** was mounted on a Rigaku R-AXIS RAPID diffractometer. Data collection was performed at room temperatures (T=295 K). Crystal data for **7c**: $4(C_{20}H_{21}N_3O_2)\cdot C_2H_3N$, F.W. 1382.64, triclinic $P\bar{1}$ (No. 2), a=11.0696(15) Å, b=12.6340(16) Å, c=14.8683(19) Å, α=99.133(6)°, β=98.061(5)°, γ=107.516(6)°, V=1918.4(4) Å^3, Z=1, $D_{(calcd)}$=1.197 [mg/m^3]. Initial structure model was obtained by SHELXS-97,[35] completed by successive difference Fourier syntheses and refined to convergence by SHELXL-97,[35] final R_1=0.0488, wR^2=0.1472, for 4857 observations. An alternative model refinement proved to be futile in the acentric $P1$ space group. Crystallographic data for **7c** have been deposited at the Cambridge Crystallographic Data centre under deposition no. CCDC 801193. Copies of these data can be obtained free of charge upon application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: 00 44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

2,3-Dihydro-2,2-dimethylimidazo[2,1-*a*]phthalazin-4-ium-6-olate (**3**) and (*S*)-2,3-dihydro-2-isopropyl-imidazo[2,1-*a*]phthalazin-4-ium-6-olate (**8**) are described compounds.[28] 2,3-Dihydrobenzo[*g*]imidazo[2,1-*a*]phthalazin-4-ium-6-olates (**4**, **9**, **10** and **11**) were synthesized in four steps (i–iv) starting from the anhydride of naphthalene-2,3-dicarboxylic acid and the corresponding aminoalcohol [2-amino-2-methylpropan-1-ol, (*S*)-2-amino-3-methylbutan-1-ol and (*S*)-2-amino-2-phenylethanol and *rac*-2-aminobutan-1-ol]. (The details are described in the Supplementary data.)

4.3. General procedure for the anhydride-induced transformation of zwitterions

A mixture of the zwitterion **3**, **4**, **9**, **10** or **11** (10 mmol) and the corresponding anhydride (100 mL) was heated to reflux for 1.5–5 h. The excess of the anhydride was distilled under reduced pressure and the resulted brownish solid was stirred and triturated with cold saturated $NaHCO_3$ solution (20 mL), which was then decanted. The residue was then triturated with ethanol to obtain yellowish white powder, which was filtered off, thoroughly washed with water and dried over P_2O_5 in a vacuum desiccator. The composition of the crude product was checked by TLC on silica plate (DCM/MeOH 80/1) and ^{1}H NMR spectroscopy. After the acetic anhydride-induced reactions of **9**–**11**, which were conducted for 1.5 h, two components (*exo*/*endo* diastereomeric pairs **13a***/**13a**, **15a***/**15a** and **16a***/**16a**) were clearly discernible in the primarily isolated substances. Their separation was performed by flash column chromatography on silica using DCM/MeOH 100/1 as eluent. After the evaporation of the first and second bands the oily residues were crystallized by water to obtain the *exo*- and *endo* products, respectively. Analytical samples were recrystallized from EtOH. Analytical and spectroscopic data of **12a**, **12b** and **14a** (yield: 59%, 55%, and 48% with reaction time of 2 h) are reported in Ref. 28.

*4.3.1. 3-Butyryl-1-ethyl-1,2,3,3a,4,5,6,6a-octahydro-5,5-dimethyl-3,3a,5a-triazapentaleno[3a,3-a]inden-2,6(3H,5aH)-dione (**5c**).* Yield: 1.74 g, 49% (reaction time: 5 h); white solid, mp 114–115 °C; R_f (DCM/MeOH 80/1) 0.71; ν_{max} 1753, 1699 (broad), 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.76 (1H, m, H7), 7.54–7.49 (2H, m, H8,9), 7.20 (1H, m, H10), 4.19 (1H, d, J 9.5 Hz, H4$_{exo}$), 3.67 (1H, d, J 9.5 Hz, H4$_{endo}$), 3.42 (1H, dd, J 8.3, 6.1 Hz, H1), 2.98 (2H, m, COCH_2CH$_2$CH$_3$), 1.83–1.79 (3H, overlapping ms, COCH$_2$CH_2CH$_3$ and 1-CH_AH$_B$CH$_3$), 1.76 (3H, s, 5-CH_{3exo}), 1.74 (3H, s, 5-CH_{3endo}), 1.26 (1H, m, 1-CH$_A$$H_BCH_3$), 1.06 (3H, t, J 7.3 Hz, COCH$_2$CH$_2$CH_3), 0.77 (3H, t, J 7.6 Hz, 1-CH$_2$CH_3); ^{13}C NMR ($CDCl_3$) δ 173.5 (C6), 173.3 (C2), 170.5 (*C*OCH$_2$CH$_2$CH$_3$), 143.0 (10a), 134.1 (6a), 132.7 (C9), 130.7 (C8), 124.7 (C7), 122.2 (C10), 91.3 (10b), 73.1 (C4), 61.0 (C5), 49.1 (C1), 39.1 (COCH_2CH$_2$CH$_3$), 29.9 (5-*C*H$_{3exo}$), 26.3 (5-*C*H$_{3endo}$), 19.8 (1-*C*H$_2$CH$_3$), 18.5 (COCH$_2$CH_2CH$_3$), 14.1 (COCH$_2$CH$_2$CH_3), 12.0 (1-CH$_2$*C*H$_3$). Anal. Calcd for $C_{20}H_{25}N_3O_3$ (355.43): C, 67.58; H, 7.09; N, 11.82. Found: C, 67.64; H, 7.01; N, 11.77%.

*4.3.2. 3-Acetyl-1,2,3,3a,4,5,6,6a-octahydro-5,5-dimethyl-3,3a,5a-triazabenzo[f]pentaleno[3a,3-a]inden-2,6(3H,5aH)-dione (**6a**).* Yield: 3.21 g, 92% (reaction time: 5 h); white solid, mp 246–248 °C; R_f (DCM/MeOH 80/1) 0.44; ν_{max} 1746, 1707 (broad), 1641 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.30 (1H, s, H7), 8.00 (1H, d, J 8.3 Hz, H8), 7.91 (1H, d, J 8.3 Hz, H11), 7.80 (1H, s, H12), 7.63 (1H, t, J 8.3 Hz, H10), 7.59 (1H, t, J 8.3 Hz, H9), 4.19 (1H, d, J 9.7 Hz, H4$_{exo}$), 3.70 (1H, d, J 18.0 Hz, H1$_{endo}$), 3.30 (1H, d, J 9.7 Hz, H4$_{endo}$), 3.03 (1H, d, J 18.0 Hz, H1$_{exo}$), 2.63 (3H, s, COCH_3), 1.74 (3H, s, 5-CH_{3exo}); 1.72 (3H, s, 5-CH_{3endo}); ^{13}C NMR ($CDCl_3$) δ 171.4 (C2), 170.2 (C6), 167.0 (*C*OCH$_3$), 142.2 (C12a), 136.1 (C11a), 134.2 (C7a), 132.3 (C6a), 130.2 (C8), 129.0 (C11), 128.9 (C10), 127.8 (C9), 125.4 (C7), 120.1 (C12), 87.1 (C12b), 73.7 (C4), 61.5 (C5), 42.4 (C1), 29.6 (5-*C*H$_{3exo}$), 25.9 (5-CH$_{3endo}$), 25.1 (CO*C*H$_3$). Anal. Calcd for $C_{20}H_{19}N_3O_3$ (349.38) C, 68.75; H, 5.48; N, 12.03. Found: C, 68.79; H, 5.53; N, 11.97%.

4.3.3. (1R,10bR*)-1,2,3,3a,4,5,6,6a-Octahydro-1,5,5-trimethyl-3-propanoyl-3,3a,5a-benzo[f]triazapentaleno[3a,3-a]inden-2,6(3H,5aH)-dione (**6b**).* Yield: 2.45 g, 65% (reaction time: 5 h); white solid, mp 256–259 °C; R_f (DCM/MeOH 80/1) 0.52; ν_{max} 1777, 1698, 1639 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.32 (1H, s, H7), 8.02 (1H, d, J 8.3 Hz, H8), 7.89 (1H, d, J 8.3 Hz, H11), 7.68 (1H, s, H12), 7.63 (1H, t, J 8.3 Hz, H10), 7.59 (1H, t, J 8.3 Hz, H9), 4.27 (1H, d, J 9.7 Hz, H4$_{exo}$), 3.67 (1H, quartet, J 7.3 Hz, H1$_{endo}$), 3.36 (1H, d, J 9.7 Hz, H4$_{endo}$), 2.96 (2H, quartet, J 7.2 Hz, COCH_2CH$_3$), 1.73 (6H, s, 5-CH_{3exo} and 5-CH_{3endo}), 1.21 (3H, t, J 7.2 Hz, COCH$_2$CH_3), 0.88 (3H, d, J 7.3 Hz, 1-CH_3); ^{13}C NMR ($CDCl_3$) δ 173.6 (*C*OCH$_2$CH$_3$), 172.2 (C2), 170.4 (C6), 138.1 (C12a), 135.8 (C11a), 134.4 (C7a), 132.0 (C6a), 130.2 (C8), 129.1 (C11), 128.9 (C10), 127.8 (C9), 125.6 (C7), 122.1 (C12); 91.2 (C12b), 73.2 (C4), 61.7 (C5), 43.9 (C1), 30.4 (COCH_2CH$_3$), 29.8 (5-*C*H$_{3exo}$), 26.1 (5-*C*H$_{3endo}$), 9.1 (COCH$_2$*C*H$_3$), 8.6 (1-*C*H$_3$). Anal. Calcd for $C_{22}H_{23}N_3O_3$ (377.43) C, 70.01; H, 6.14; N, 11.13. Found: C, 70.12; H, 6.04; N, 11.08%.

4.3.4. (1R,10bR*)-3-Butyryl-1-ethyl-1,2,3,3a,4,5,6,6a-octahydro-5,5-dimethyl-3,3a,5a-triazabenzo[f]pentaleno[3a,3-a]inden-2,6(3H,5aH)-dione (**6c**).* Yield: 2.55 g, 63% (reaction time: 5 h); white solid, mp 267–269 °C; R_f (DCM/MeOH 80/1) 0.71; ν_{max} 1774, 1697, 1636 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.32 (1H, s, H7), 8.01 (1H, d, J 8.3 Hz, H8), 7.88 (1H, d, J 8.3 Hz, H11), 7.63 (1H, s, H12) overlapped by 7.63 (1H, t, J 8.3 Hz, H10), 7.59 (1H, t, J 8.3 Hz, H9), 4.23 (1H, d, J 9.7 Hz, H4$_{exo}$), 3.41 (1H, d, J 9.7 Hz, H4$_{endo}$), 3.45 (1H, dd, J 8.3, 6.1 Hz, H1), 2.97 (2H, m, COCH_2CH$_2$CH$_3$), 1.83–1.79 (3H, overlapping ms, COCH$_2$CH_2CH$_3$ and 1-CH_AH$_B$CH$_3$), 1.76 (3H, s, 5-CH_{3exo}), 1.75 (3H, s, 5-CH_{3endo}), 1.22 (1H, m, 1-CH$_A$$H_BCH_3$), 1.06 (3H, t, J 7.3 Hz, COCH$_2$CH$_2$CH_3), 0.79 (3H, t, J 7.6 Hz, 1-CH$_2$CH_3); ^{13}C NMR ($CDCl_3$) δ 173.3 (C2), 170.5 (*C*OCH$_2$CH$_2$CH$_3$) 170.2 (C6), 137.5 (C12a), 135.3 (C11a), 134.3 (C7a),

131.7 (C6a), 130.2 (C8), 128.9 (two coalesced lines, C10,11), 127.8 (C9), 125.5 (C7), 121.5 (C12), 91.3 (12b), 72.9 (C4), 61.9 (C5), 49.7 (C1), 39.1 ($COCH_2CH_2CH_3$), 29.9 (5-CH_{3exo}), 26.5 (5-CH_{3endo}), 19.8 (1-CH_2CH_3), 18.4 ($COCH_2CH_2CH_3$), 14.1 ($COCH_2CH_2CH_3$), 12.0 (1-CH_2CH_3). Anal. Calcd for $C_{24}H_{27}N_3O_3$ (405.49) C, 71.09; H, 6.71; N, 10.36. Found: C, 71.00; H, 6.74; N, 10.46%.

*4.3.5. (5S,10bR)-3-Butyryl-1-ethyl-1,2,3,3a,4,5,6,6a-octahydro-5-iso-propyl-3,3a,5a-triazapentaleno[3a,3-a]inden-2,6(3H,5aH)-dione (**12c**).* Yield: 1.59 g, 43% (reaction time: 2 h); white solid, mp 94–97 °C; R_f (DCM/MeOH 80/1) 0.69; $[\alpha]_D^{25}$ −64.9 (*c* 0.6, EtOH); ν_{max} 1765, 1704, 1691, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.81 (1H, m, H7), 7.60–7.50 (2H, m, H8,9), 7.22 (1H, m, H10), 4.51 (1H, dd, *J* 10.1, 8.3 Hz, $H4_{exo}$), 3.98 (1H, dt, *J* 9.9, 8.3 Hz, H5), 3.34 (1H, dd, *J* 9.2, 5.3 Hz, H1), 3.09 (1H, dd, *J* 10.1, 8.3 Hz, $H4_{endo}$), 2.90 (2H, m, $COCH_2CH_2CH_3$), 1.97 [1H, m, $CH(CH_3)_2$], 1.92 (1H, m, 1-$CH_AH_BCH_3$), 1.74 (2H, m, $COCH_2CH_2CH_3$), 1.33 (1H, m, 1-$CH_AH_BCH_3$), 1.22 [3H, d, *J* 6.9 Hz, CH(CH_3)(CH_3)], 1.04 [3H, d, *J* 6.9 Hz, CH(CH_3)(CH_3)], 1.01 (3H, t, *J* 7.3 Hz, $COCH_2CH_2CH_3$), 0.80 (3H, t, *J* 7.7 Hz, 1-CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 173.7 (C6), 173.0 (C2), 170.3 ($COCH_2CH_2CH_3$), 142.8 (C10a), 133.0 (C9), 132.5 (C6a), 130.9 (C8), 125.3 (C7), 122.5 (C10), 90.0 (C10b), 64.4 (C4), 62.8 (C5), 48.3 (C1), 39.0 ($COCH_2CH_2CH_3$), 36.2 [$CH(CH_3)_2$], 20.8 CH(CH_3)(CH_3)], 20.0 CH(CH_3)(CH_3)], 19.4 (1-CH_2CH_3), 18.3 ($COCH_2CH_2CH_3$), 14.1 ($COCH_2CH_2CH_3$), 11.8 4 (1-CH_2CH_3). Anal. Calcd for $C_{21}H_{27}N_3O_3$ (369.46): C, 68.27; H, 7.37; N, 11.37. Found: C, 68.39; H, 7.44; N, 11.24%.

*4.3.6. (5S,12bR)-3-Acetyl-1,2,3,3a,4,5,6,6a-octahydro-5-iso-propyl-3,3a,5a-triazabenzo[f]pentaleno[3a,3-a]inden-2,6(3H,5aH)-dione (**13a**).* Yield: 1.13 g, 31% (reaction time: 1.5 h); pale yellowish solid, 2.23 g, 61% (reaction time: 5 h); mp 227–230 °C; R_f (DCM/MeOH 80/1) 0.60; $[\alpha]_D^{25}$ −70.1 (*c* 0.8, DMSO); ν_{max} 1754, 1720, 1693, 1641 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.30 (1H, s, H7), 8.00 (1H, d, *J* 8.3 Hz, H8), 7.92 (1H, d, *J* 8.3 Hz, H11), 7.80 (1H, s, H12), 7.63 (1H, t, *J* 8.3 Hz, H10), 7.60 (1H, t, *J* 8.3 Hz, H9), 4.46 (1H, dd, *J* 10.5, 7.8 Hz, $H4_{exo}$), 4.04 (1H, dt, *J* 10.4, 7.8 Hz, H5), 3.62 (1H, d, *J* 18.0 Hz, $H1_{endo}$), 3.20 (1H, d, *J* 18.0 Hz, $H1_{exo}$), 3.06 (1H, dd, *J* 10.5, 7.8 Hz, $H4_{endo}$), 2.61 (3H, s, $COCH_3$), 1.96 [1H, m, $CH(CH_3)_2$], 1.22 [3H, d, *J* 6.8 Hz, CH(CH_3)(CH_3)], 1.05 [3H, d, *J* 6.8 Hz, CH(CH_3)(CH_3)]; ^{13}C NMR ($CDCl_3$) δ 173.3 (C6), 171.5 (C2), 167.1 ($COCH_3$), 141.8 (C12a), 136.2 (C11a), 134.4 (C7a), 130.3 (C8), 129.1 (C11), 128.9 (C10), 128.7 (C6a), 127.8 (C9), 125.7 (C7), 120.7 (C12), 85.8 (C12b), 64.6 (C4), 62.9 (C5), 41.1 (C1), 35.7 [$CH(CH_3)_2$], 25.1 ($COCH_3$), 20.9 [CH(CH_3)(CH_3)], 19.5 CH(CH_3)(CH_3)]. Anal. Calcd for $C_{21}H_{21}N_3O_3$ (363.41) C, 69.41; H, 5.82; N, 11.56. Found: C, 69.34; H, 5.88; N, 11.55%.

*4.3.7. (5S,12bS)-3-Acetyl-1,2,3,3a,4,5,6,6a-octahydro-5-iso-propyl-3,3a,5a-triazabenzo[f]pentaleno[3a,3-a]inden-2,6(3H,5aH)-dione (**13a***).* Yield: 1.02 g, 28% (reaction time: 1.5 h); white solid, mp 213–215 °C; R_f (DCM/MeOH 80/1) 0.50; $[\alpha]_D^{25}$ +63.2 (*c* 0.6, EtOH); ν_{max} 1767, 1702, 1681, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.27 (1H, s, H7), 7.99 (1H, d, *J* 8.3 Hz, H8), 7.92 (1H, d, *J* 8.3 Hz, H11), 7.87 (1H, s, H12), 7.62 (1H, t, *J* 8.3 Hz, H10), 7.58 (1H, t, *J* 8.3 Hz, H9), 3.73 (1H, dd, *J* 11.5, 7.1 Hz, $H4_{exo}$), 3.84 (1H, quartet, *J* 7.6, H5), 3.56 (1H, d, *J* 18.6 Hz, $H1_{endo}$), 3.27 (1H, dd, *J* 11.5, 7.1 Hz, $H4_{endo}$), 3.22 (1H, d, *J* 18.6 Hz, $H1_{exo}$), 3.09 [1H, m, $CH(CH_3)_2$], 2.62 (3H, s, $COCH_3$), 1.27 [3H, d, *J* 6.9 Hz, CH(CH_3)(CH_3)], 0.89 [3H, d, *J* 6.8 Hz, CH(CH_3)(CH_3)]; ^{13}C NMR ($CDCl_3$) δ 171.0 (C2), 169.0 (C6), 167.1 ($COCH_3$), 141.3 (C12a), 136.2 (C11a), 134.2 (C7a), 130.2 (C8), 130.1 (C6a), 129.0 (C11), 128.9 (C10), 127.7 (C9), 125.2 (C7), 121.0 (C12), 86.5 (C12b), 63.6 (C5), 62.9 (C4), 41.1 (C1), 26.2 [$CH(CH_3)_2$], 25.1 ($COCH_3$), 22.3 [CH(CH_3)(CH_3)], 18.6 CH(CH_3)(CH_3)]. Anal. Calcd for $C_{21}H_{21}N_3O_3$ (363.41) C, 69.41; H, 5.82; N, 11.56. Found: C, 69.32; H, 5.90; N, 11.62%.

*4.3.8. (1R,5S,12bR)-1,2,3,3a,4,5,6,6a-Octahydro-1-methyl-3-propanoyl-5-iso-propyl-3,3a,5a-triazabenzo[f]pentaleno[3a,3-a]inden-2,6(3H,5aH)-dione (**13b**).* Yield: 1.72 g, 44% (reaction time: 1.5 h); pale yellowish solid, 3.05 g, 78% (reaction time: 5 h); mp 234–236 °C; R_f (DCM/MeOH 80/1) 0.61; $[\alpha]_D^{25}$ −86.0 (*c* 0.8, DMSO); ν_{max} 1739, 1710 (broad), 1634 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.33 (1H, s, H7), 8.01 (1H, d, *J* 7.9 Hz, H8), 7.89 (1H, d, *J* 7.9 Hz, H11), 7.64 (1H, t, *J* 7.9 Hz, H10), 7.62 (1H, s, H12), 7.59 (1H, t, *J* 7.9 Hz, H9), 4.52 (1H, dd, *J* 10.0, 8.0 Hz, $H4_{exo}$), 4.06 (1H, dt, *J* 9.8, 8.1 Hz, H5), 3.57 (1H, quartet, *J* 7.2 Hz, H1), 3.12 (1H, dd, *J* 10.0, 8.0 Hz, $H4_{endo}$), 3.00 (2H, quartet, *J* 7.6 Hz, $COCH_2CH_3$), 1.96 [1H, m, $CH(CH_3)_2$], 1.26 (3H, t, *J* 7.6 Hz, $COCH_2CH_3$), 1.22 [3H, d, *J* 6.8 Hz, CH(CH_3)(CH_3)], 1.10 (3H, d, *J* 7.2 Hz, 1-CH_3), 1.05 [3H, d, *J* 6.8 Hz, CH(CH_3)(CH_3)]; ^{13}C NMR ($CDCl_3$) δ 173.7 (C2), 173.5 (C6), 171.2 ($COCH_2CH_3$), 137.2 (C12a), 135.5 (C11a), 134.3 (C7a), 130.2 (C8), 129.1 (C10), 129.7 (C6a), 128.9 (C11), 127.8 (C9), 125.7 (C7), 120.7 (C12), 85.8 (C12b), 64.6 (C4), 62.9 (C5), 41.1 (C1), 35.7 [$CH(CH_3)_2$], 30.8 ($COCH_2CH_3$), 20.9 [CH(CH_3)(CH_3)], 19.5 CH(CH_3)(CH_3)], 9.5 ($COCH_2CH_3$), 8.7 (1-CH_3). Anal. Calcd for $C_{23}H_{25}N_3O_3$ (391.46) C, 70.57; H, 6.44; N, 10.73. Found: C, 70.61; H, 6.37; N, 10.80%.

*4.3.9. (5S,12bR)-3-Acetyl-1,2,3,3a,4,5,6,6a-octahydro-5-phenyl-3,3a,5a-triazabenzo[f]pentaleno[3a,3-a]inden-2,6(3H,5aH)-dione (**15a**).* Yield: 0.76 g, 19% (reaction time: 1.5 h); yellowish solid 1.91 g, 48% (reaction time: 5 h); mp 252–255 °C; R_f (DCM/MeOH 80/1) 0.57; $[\alpha]_D^{25}$ −15.9 (*c* 0.8, DMSO); ν_{max} 1774, 1705, 1694, 1648, 1612 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.43 (1H, s, H7), 8.08 (1H, d, *J* 8.0 Hz, H8), 7.98 (1H, d, *J* 8.0 Hz, H11), 7.92 (1H, s, H12), 7.70 (1H, t, *J* 8.0 Hz, H10), 7.65 (1H, t, *J* 8.0 Hz, H9), 7.50–7.43 [4H, m, H2′,3′,5′,6′ (Ph)], 7.39 [1H, m, H4′ (Ph)], 5.68 (1H, t, *J* 7.4 Hz, H5), 4.81 (1H, dd, *J* 9.9, 7.4 Hz, $H4_{exo}$), 3.59 (1H, d, *J* 18.0 Hz, $H1_{endo}$), 3.39 (1H, dd, *J* 9.9, 7.4 Hz, $H4_{endo}$), 3.22 (1H, d, *J* 18.0 Hz, $H1_{exo}$), 2.60 (3H, s, $COCH_3$); ^{13}C NMR ($CDCl_3$) δ 173.2 (C6), 171.0 (C2), 167.1 ($COCH_3$), 141.6 (C12a), 140.2 [C1′, (Ph)], 136.3 (C11a), 134.4 (C7a), 130.4 (C8), 129.5 [C3′5′, (Ph)], 129.3 (C10), 129.0 (C11), 128.5 (C6a), 128.4 [C4′, (Ph)], 128.0 (C9), 126.1 (C7), 125.6 [C2′6′, (Ph)], 121.1 (C12), 86.2 (C12b), 66.0 (C4), 58.6 (C5), 40.9 (C1), 25.1 ($COCH_3$). Anal. Calcd for $C_{24}H_{19}N_3O_3$ (397.43) C, 72.53; H, 4.82; N, 10.57. Found: C, 72.58; H, 4.71; N, 10.68%.

*4.3.10. (5S,12bS)-3-Acetyl-1,2,3,3a,4,5,6,6a-octahydro-5-phenyl-3,3a,5a-triazabenzo[f]pentaleno[3a,3-a]inden-2,6(3H,5aH)-dione (**15a***).* Yield: 0.91 g, 23% (reaction time: 1.5 h); yellowish solid, mp 240–243 °C; R_f (DCM/MeOH 80/1) 0.41; $[\alpha]_D^{25}$ +22.6 (*c* 1.1, CCl_4); ν_{max} 1768, 1703 (broad), 1632, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.19 (1H, s, H7), 8.04 (1H, d, *J* 8.1 Hz, H8), 7.96 (1H, d, *J* 8.1 Hz, H11), 7.92 (1H, s, H12), 7.71 (1H, t, *J* 8.1 Hz, H10), 7.63 (1H, t, *J* 8.1 Hz, H9), 7.39–7.34 [5H, m, H2′-6′ (Ph)], 5.18 (1H, dd, *J* 7.7, 3.4 Hz, H5), 4.30 (1H, dd, *J* 10.5, 7.7 Hz, $H4_{exo}$), 3.75 (1H, d, *J* 18.4 Hz, $H1_{endo}$), 3.79 (1H, dd, *J* 10.5, 3.4 Hz, $H4_{endo}$), 3.14 (1H, d, *J* 18.4 Hz, $H1_{exo}$), 2.65 (3H, s, $COCH_3$); ^{13}C NMR ($CDCl_3$) δ 171.3 (C2), 168.6 (C6), 167.0 ($COCH_3$), 141.3 (C12a), 140.8 [C1′, (Ph)], 136.4 (C11a), 134.1 (C7a), 130.2 (C8), 129.5 (C10), 129.3 [C3′5′, (Ph)], 129.8 (C6a), 129.1 (C11), 128.3 [C4′, (Ph)], 128.0 (C9), 125.2 (C7), 125.0 [C2′6′, (Ph)], 121.3 (C12); 86.9 (C12b), 67.7 (C5), 60.3 (C4), 41.8 (C1), 25.2 ($COCH_3$). Anal. Calcd for $C_{24}H_{19}N_3O_3$ (397.43) C, 72.53; H, 4.82; N, 10.57. Found: C, 72.64; H, 4.81; N, 10.49%.

4.3.11. (5R,12bS*)-3-Acetyl-5-ethyl-1,2,3,3a,4,5,6,6a-octahydro-3,3a,5a-triazabenzo[f]pentaleno[3a,3-a]inden-2,6(3H,5aH)-dione (**16a**).* Yield: 0.98 g, 28% (reaction time: 1.5 h); pale yellowish solid 2.52 g, 72% (reaction time: 5 h); mp 249–251 °C; R_f (DCM/MeOH 80/1) 0.58; ν_{max} 1758, 1720, 1696, 1642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.32 (1H, s, H7), 7.98 (1H, d, *J* 8.1 Hz, H8), 7.92 (1H, d, *J* 8.1 Hz, H11), 7.82 (1H, s, H12), 7.62 (1H, t, *J* 8.1 Hz, H10), 7.57 (1H, t, *J* 8.1 Hz, H9), 4.54 (1H, dd, *J* 10.0, 8.0 Hz, $H4_{exo}$), 4.29 (1H, quint, *J* 8.0 Hz, H5), 3.65 (1H, d, *J* 18.0 Hz, $H1_{endo}$), 3.20 (1H, d, *J* 18.0 Hz, $H1_{exo}$), 3.05 (1H, dd, *J* 10.0, 8.0 Hz, $H4_{endo}$), 2.63 (3H, s, $COCH_3$), 1.97 (1H, m, $CH_AH_BCH_3$), 1.79 (1H, m, $CH_AH_BCH_3$), 1.11 (3H, t, *J* 7.3 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 173.5 (C6), 171.5 (C2), 167.3 ($COCH_3$), 141.9 (C12a), 136.5

(C11a), 134.6 (C7a), 130.3 (C8), 129.2 (C11), 128.9 (C10), 128.5 (C6a), 127.8 (C9), 125.9 (C7), 120.7 (C12); 85.7 (C12b), 65.5 (C4), 58.1 (C5), 41.3 (C1), 29.8 (CH_2CH_3), 25.3 ($COCH_3$), 11.0 (CH_2CH_3). Anal. Calcd for $C_{20}H_{19}N_3O_3$ (349.38) C, 68.75; H, 5.48; N, 12.03. Found: C, 68.72; H, 5.59; N, 11.92%.

4.3.12. (5R,12bR*)-3-Acetyl-5-ethyl-1,2,3,3a,4,5,6,6a-octahydro-3,3a,5a-triazabenzo[f]pentaleno[3a,3-a]inden-2,6(3H,5aH)-dione (**16a***).* Yield: 1.26 g, 36% (reaction time: 1.5 h); pale yellowish solid, mp 237–240 °C; R_f (DCM/MeOH 80/1) 0.46; ν_{max} 1770, 1704, 1680, 1642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.30 (1H, s, H7), 8.01 (1H, d, *J* 8.3 Hz, H8), 7.91 (1H, d, *J* 8.2 Hz, H11), 7.88 (1H, s, H12), 7.63 (1H, t, *J* 8.2 Hz, H10), 7.58 (1H, t, *J* 8.2 Hz, H9), 3.74 (1H, dd, *J* 11.0, 7.2 Hz, $H4_{exo}$), 3.86 (1H, quartet, *J* 7.2, H5), 3.58 (1H, d, *J* 18.3 Hz, $H1_{endo}$), 3.27 (1H, dd, *J* 11.0, 7.2 Hz, $H4_{endo}$), 3.22 (1H, d, *J* 18.3 Hz, $H1_{exo}$), 2.60 (3H, s, $COCH_3$), 2.57 (2H, quint, *J* 7.2 Hz, CH_2CH_3), 1.04 (2H, quint, *J* 7.2 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 171.1 (C2), 169.3 (C6), 167.1 ($COCH_3$), 141.6 (C12a), 136.3 (C11a), 134.2 (C7a), 130.4 (C8), 130.2 (C6a), 129.0 (C11), 128.8 (C10), 127.8 (C9), 125.4 (C7), 121.2 (C12), 86.6 (C12b), 62.1 (C4), 58.9 (C5), 41.4 (C1), 30.9 (CH_2CH_3), 25.3 ($COCH_3$), 11.4 (CH_2CH_3). Anal. Calcd for $C_{20}H_{19}N_3O_3$ (349.38) C, 68.75; H, 5.48; N, 12.03. Found: C, 68.81; H, 5.54; N, 12.12%.

4.3.13. (1R,5S*,12bR*)-5-Ethyl-1,2,3,3a,4,5,6,6a-octahydro-1-methyl-3-propanoyl-3,3a,5a-triazabenzo[f]pentaleno[3a,3-a]inden-2,6(3H,5aH)-dione (**16b**).* Yield: 1.40 g, 28% (reaction time: 1.5 h); white solid 3.02 g, 80% (reaction time: 5 h); mp 268–261 °C; R_f (DCM/MeOH 80/1) 0.65; ν_{max} 1741, 1710 (broad), 1631 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.30 (1H, s, H7), 7.97 (1H, d, *J* 8.1 Hz, H8), 7.85 (1H, d, *J* 8.1 Hz, H11), 7.59 (1H, t, *J* 8.1 Hz, H10), 7.56 (1H, s, H12), overlapped with 7.55 (1H, t, *J* 8.1 Hz, H9), 4.53 (1H, dd, *J* 10.0, 8.2 Hz, $H4_{exo}$), 4.29 (1H, quint, *J* 8.2 Hz, H5), 3.54 (1H, quartet, *J* 7.2 Hz, H1), 3.05 (1H, dd, *J* 10.0, 8.2 Hz, $H4_{endo}$), 2.96 (2H, quartet, *J* 7.4 Hz, $COCH_2CH_3$), 1.97 (1H, m, $CH_AH_BCH_3$), 1.79 (1H, m, $CH_AH_BCH_3$), 1.26 (3H, t, *J* 7.4 Hz, $COCH_2CH_3$), 1.11 (3H, t, *J* 7.3 Hz, CH_2CH_3), 1.04 (3H, d, *J* 7.2 Hz, 1-CH_3); ^{13}C NMR ($CDCl_3$) δ 173.9 (C6), 173.4 (C2), 171.4 ($COCH_2CH_3$), 137.7 (C12a), 135.8 (C11a), 134.3 (C7a), 130.0 (C8), 129.4 (C10), 129.6 (C6a), 128.5 (C11), 127.6 (C9), 125.2 (C7), 120.7 (C12), 85.3 (C12b), 65.4 (C4), 58.2 (C5), 41.5 (C1), 30.6 ($COCH_2CH_3$), 29.8 (CH_2CH_3), 9.5 ($COCH_2CH_3$), 8.8 (1-CH_3). Anal. Calcd for $C_{22}H_{23}N_3O_3$ (377.44) C, 70.01; H, 6.14; N, 11.13. Found: C, 69.91; H, 6.22; N, 11.06%.

4.4. General procedure for the hydrazinolysis of tetra- and pentacycles 5c, 6a–c, 12a–c, 13a,b, 14a, 15a, 16a,b, 13a*, 15a* and 16a* (method A)

To a suspension of the corresponding precursor (2 mmol) in EtOH (10 mL) was added 92% $N_2H_4 \cdot H_2O$ (200 μL dissolved in 1 mL of EtOH) dropwise under Ar atmosphere at rt, and the mixture was stirred and refluxed for 15 min. The resulted yellow solution was cooled with ice-water, neutralized with a few drops of AcOH, and after standing ca. 30 min in refrigerator the precipitated crystals were filtered off and washed with water. The composition of the crude product was checked by TLC on silica plate (DCM/MeOH 20/1) and ^1H NMR spectroscopy. After the reactions of **13a** and **15a** two components (**18a**/**21a** and **19a**/**24a**) were clearly discernible in the primarily isolated substances. Their separation was performed by flash column chromatography on silica using DCM/MeOH 30/1 as eluent. After the evaporation of the first and second bands the solid residues were washed with water and filtered off to obtain the N3-deacylated- and diazocine products, respectively. Following the reaction of **12b** no any solid was precipitated from the neutralized reaction mixture, which was then evaporated. The oily residue was triturated with acetone to obtain a white solid composed of **17b** and **21b**. After filtration of this mixture the evaporation of the acetonic solution gave oily residue, which was slowly solidified by the trituration with water and filtered off to obtain **26b** as a white powder. The separation of **17b** and **21b** was performed by flash column chromatography on silica using DCM/MeOH 30/1 as eluent. Analytical samples were obtained by recrystallization from EtOH and dried in a vacuum desiccator over P_2O_5.

*4.4.1. (Z)-1-Ethyl-4,5-dihydro-2-hydroxy-5,5-dimethylpyrazolo[1,5-d]benzo[f][1,4]diazocin-7(6H)-one (**2c**).* Yield: 0.126 g, 22%; white solid, mp 242–246 °C; R_f (DCM/MeOH 20/1) 0.18; ν_{max} ~3300–2200, 1600, 1513 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.72 (1H, br s, OH), 7.69 (1H, s, NH), 7.62–7.53 (3H, m, H8-10), 7.31 (1H, m, H11), 3.78 (1H, d, *J* 15.2 Hz, $H4_{exo}$), 3.51 (1H, d, *J* 15.2 Hz, $H4_{endo}$), 2.33 (1H, dquartet, *J* 14.1, 7.5 Hz, 1-$CH_AH_BCH_3$), 2.25 (1H, dquartet, *J* 14.1, 7.5 Hz, 1-$CH_AH_BCH_3$), 1.38 (3H, s, 5-CH_{3exo}), 1.15 (3H, s, 5-CH_{3endo}), 1.02 (3H, t, *J* 7.5 Hz, 1-CH_2CH_3); ^{13}C NMR (DMSO-d_6) δ 171.0 (C7), 159.2 (C2), 140.1 (C7a), 139.9 (C11b), 130.6 (C10), 130.1 (C9), 129.71, 129.65 (C8,11), 127.6 (C11a), 104.6 (C1), 56.2 (C4), 55.0 (C5), 29.7 (5-CH_{3exo}), 29.3 (5-CH_{3endo}), 15.98 (1-CH_2CH_3), 15.92 (1-CH_2CH_3) (the two latter hardly separated lines were identified by DEPT-135 measurement). Anal. Calcd for $C_{16}H_{19}N_3O_2$ (285.34) C, 67.35; H, 6.71; N, 14.73. Found: C, 67.30; H, 6.79; N, 14.85%.

*4.4.2. (Z)-4,5-Dihydro-2-hydroxy-5,5-dimethylpyrazolo[1,5-d]naphtho[2,3-f][1,4]diazocin-7(6H)-one (**7a**).* Yield: 0.295 g, 48%; white solid, mp 369–359 °C; R_f (DCM/MeOH 20/1) 0.13; ν_{max} 3270, 3204, ~3100–2400, 1643, 1568, 1510 cm^{-1}; ^1H NMR (DMSO-d_6) 9.92 (1H, br s, OH), 8.10 (1H, s, H8), 8.05 (1H, s, NH), 8.07 (1H, m, H9), 8.02 (1H, m, H12), 7.85 (1H, s, H13), 7.63–7.59 (2H, m, H10,11), 5.64 (1H, s, H1), 3.79 (1H, d, *J* 15.4 Hz, $H4_{exo}$), 3.51 (1H, *J* 15.4 Hz, $H4_{endo}$), 1.30 (3H, s, 5-CH_{3endo}), 1.10 (3H, s, 5-CH_{3exo}); ^{13}C NMR (DMSO-d_6) δ 171.6 (C7), 162.0 (C2), 142.0 (C13b), 134.8 (C7a), 134.0 (12a), 133.4 (C8a), 129.6 (C8), 129.1 (C9), 128.9 (12), 128.4 (C11), 128.1 (C10), 127.3 (C13), 126.9 (C13a), 96.4 (C1), 56.1 (C4), 55.0 (C5), 29.8 (5-CH_{3endo}), 29.1 (5-CH_{3exo}); ^{15}N NMR (DMSO-d_6) δ 272 (N3), 184 (N3a), 137 (N6). Anal. Calcd for $C_{18}H_{17}N_3O_2$ (307.35) C, 70.34; H, 5.58; N, 13.67. Found: C, 70.39; H, 5.51; N, 13.58%.

*4.4.3. (Z)-4,5-Dihydro-2-hydroxy-1,5,5-trimethylpyrazolo[1,5-d]naphtho[2,3-f][1,4]diazocin-7(6H)-one (**7b**).* Yield: 0.270 g, 48%; white solid, mp 356–359 °C; R_f (DCM/MeOH 20/1) 0.15; ν_{max} 3272, 3210, ~3100–2400, 1645, 1556, 1509 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.82 (1H, br s, OH), 8.11 (1H, s, H8), 8.07 (1H, m, H9), 8.05 (1H, m, H12), 7.94 (1H, s, NH), 7.82 (1H, s, H13), 7.63–7.59 (2H, m, H10,11), 3.74 (1H, d, *J* 15.4 Hz, $H4_{exo}$), 3.50 (1H, *J* 15.4 Hz, $H4_{endo}$), 1.67 (3H, s, 1-CH_3), 1.34 (3H, s, 5-CH_{3exo}), 1.12 (3H, s, 5-CH_{3endo}); ^{13}C NMR (DMSO-d_6) δ 170.9 (C7), 160.0 (C2), 140.0 (C13b), 138.1 (C7a), 133.7 (C12a), 133.4 (C8a), 129.5 (C8), 129.0 (two coalesced lines C9,13), 128.9 (C12), 128.4 (C10), 128.2 (C11), 125.6 (C13a), 102.0 (C1), 56.1 (C4), 55.0 (C5), 29.6 (5–CH_{3exo}), 29.2 (5-CH_{3endo}), 8.1 (1-CH_3); ^{15}N NMR (DMSO-d_6) 272 (N3), 183 (N3a), 138 (N6). Anal. Calcd for $C_{19}H_{19}N_3O_2$ (321.37) C, 71.01; H, 5.96; N, 13.08. Found: C, 71.14; H, 6.16; N, 13.02%.

*4.4.4. (Z)-1-Ethyl-4,5-dihydro-2-hydroxy-5,5-dimethylpyrazolo[1,5-d]naphtho[2,3-f][1,4]diazocin-7(6H)-one (**7c**).* Yield: 0.134 g, 20%; white solid, mp 310–312 °C; R_f (DCM/MeOH 20/1) 0.17; ν_{max} 3178, 3049, ~2950–2300, 1646, 1558, 1508 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.71 (1H, br s, OH), 8.11 (1H, s, H8), 8.07 (1H, m, H9), 8.04 (1H, m, H12), 7.85 (1H, s, H13), 7.65 (1H, s, NH), 7.63–7.59 (2H, m, H10,11), 3.73 (1H, d, *J* 15.2 Hz, $H4_{exo}$), 3.49 (1H, d, *J* 15.2 Hz, $H4_{endo}$), 2.38 (1H, dquartet, *J* 14.6, 7.5 Hz, 1-$CH_AH_BCH_3$), 2.29 (1H, dquartet, *J* 14.6, 7.5 Hz, 1-$CH_AH_BCH_3$), 1.37 (3H, s, 5-CH_{3exo}), 1.13 (3H, s, 5-CH_{3endo}), 1.01 (3H, t, *J* 7.5 Hz, 1-CH_2CH_3); ^{13}C NMR (DMSO-d_6) δ 171.1 (C7), 159.7 (C2), 140.0 (C13b), 137.9 (C7a), 133.6 (C12a), 133.4 (C8a), 129.4 (C8), 129.2 (C9), 129.0 (C13), 128.9 (C12), 128.4 (C10), 128.2 (C11), 125.5 (C13a), 104.9 (C1), 56.2 (C4), 54.8 (C5), 29.6 (5-CH_{3exo}), 29.4

(5-CH_{3endo}), 16.07 (1-CH_2CH_3), 16.05 (1-CH_2CH_3) (the two latter hardly separated lines were identified by DEPT-135 measurement); ^{15}N NMR (DMSO-d_6) 275 (N3), 181 (N3a), 137 (N6). Anal. Calcd for $C_{20}H_{21}N_3O_2$ (335.40) C, 71.62; H, 6.31; N, 12.53. Found: C, 71.68; H, 6.40; N, 12.42%.

*4.4.5. (5S,10bR)-1,2,3,3a,4,5,6,6a-octahydro-1-methyl-5-iso-propyl-3,3a,5a-triazapentaleno[3a,3-a]inden-2,6(3H,5aH)-dione (**17b**).* Yield: 0.090 g, 15%; white solid, mp 210–212 °C; R_f (DCM/MeOH 20/1) 0.36; $[\alpha]_D^{25}$ −26.4 (*c* 1.2, DMSO); ν_{max} 3250, 1700, 1610, 1544 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.95 (1H, s, NH), 7.70 (1H, d, *J* 7.6 Hz, H7), 7.66 (1H, t, *J* 7.6 Hz, H9), 7.59 (1H, t, *J* 7.6 Hz, H8), 3.97 (1H, dd, *J* 10.0, 8.1 Hz, H4$_{exo}$), 3.67 (1H, m, H5), 3.46 (1H, qa, *J* 7.3 Hz, H1), 3.29 (1H, dd, *J* 10.0, 8.9 Hz, H4$_{endo}$), 2.02 [1H, m, C*H*(CH$_3$)$_2$], 1.07 [3H, d, *J* 6.5 Hz, CH(C*H*$_3$)(CH$_3$)], 0.91 [3H, d, *J* 6.5 Hz, CH(CH$_3$)(C*H*$_3$)], 0.79 (1H, d, *J* 7.3 Hz, 1-CH$_3$); ^{13}C NMR (DMSO-d_6) δ 176.5 (C2), 173.8 (C6), 144.4 (C10a), 133.5 (C9), 131.9 (C6a), 131.0 (C8), 124.8 (C7), 123.5 (C10), 94.4 (C10b), 65.8 (C4), 63.4 (C5), 38.9 (C1), 34.8 [*C*H(CH$_3$)$_2$], 21.6 [CH(*C*H$_3$)(CH$_3$)], 19.8 [CH(CH$_3$)(*C*H$_3$)], 9.5 (1-*C*H$_3$). Anal. Calcd for $C_{16}H_{19}N_3O_2$ (285.34) C, 67.35; H, 6.71; N, 14.73. Found: C, 67.46; H, 6.79; N, 14.67%.

*4.4.6. (5S,10bR)-1,2,3,3a,4,5,6,6a-octahydro-5-iso-propyl-3,3a,5a-triazabenzo[f]pentaleno[3a,3-a]inden-2,6(3H,5aH)-dione (**18a**).* Yield: 0.244 g, 38%; pale yellow solid, mp 270–274 °C; R_f (DCM/MeOH 20/1) 0.32; $[\alpha]_D^{25}$ −17.7 (*c* 1.0, DMSO); ν_{max} 3260, 1698, 1605, 1572 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.03 (1H, s, NH), 8.31 (1H, s, H7), 8.14 (1H, d, *J* 8.1 Hz, H8), 8.11 (1H, d, *J* 8.1 Hz, H11), 7.99 (1H, s, H12), 7.64 (1H, t, *J* 8.1 Hz, H10), 7.59 (1H, t, *J* 8.1 Hz, H9), 3.81 (1H, dd, *J* 10.7, 7.2 Hz, H4$_{exo}$), 3.72 (1H, dt, *J* 10.0, 7.2 Hz, H5), 3.35 (1H, d, *J* 17.6 Hz, H1$_{endo}$), 3.12 (1H, dd, *J* 10.7, 7.2 Hz, H4$_{endo}$), 2.76 (1H, d, *J* 17.6 Hz, H1$_{exo}$), 2.01 [1H, m, C*H*(CH$_3$)$_2$], 1.06 [3H, d, *J* 6.5 Hz, CH(C*H*$_3$)(CH$_3$)], 0.92 [3H, d, *J* 6.5 Hz, CH(CH$_3$)(C*H*$_3$)]; ^{13}C NMR (DMSO-d_6) δ 173.6 (C2), 173.2 (C6), 143.6 (C12a), 136.3 (C11a), 134.2 (C7a), 130.6 (C8), 129.50, 129.44 (C10,C11), 129.0 (C6a), 128.0 (C9), 124.9 (C7), 121.6 (C12), 90.2 (C12b), 65.7 (C4), 63.6 (C5), 39.2 (C1), 34.1 [*C*H(CH$_3$)$_2$], 21.7 [CH(*C*H$_3$)(CH$_3$)], 19.9 [CH(CH$_3$)(*C*H$_3$)]. Anal. Calcd for $C_{19}H_{19}N_3O_2$ (321.37) C, 71.01; H, 5.96; N, 13.08. Found: C, 71.10; H, 6.06; N, 13.01%.

*4.4.7. (5S,10bR)-1,2,3,3a,4,5,6,6a-octahydro-5-phenyl-3,3a,5a-triazabenzo[f]pentaleno[3a,3-a]inden-2,6(3H,5aH)-dione (**19a**).* Yield: 0.121 g, 17%; yellowish solid, mp 288–292 °C; R_f (DCM/MeOH 20/1) 0.27; $[\alpha]_D^{25}$ −22.5 (*c* 1.0, DMSO); ν_{max} 3276, 1703, 1615, 1588 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.97 (1H, s, NH), 8.44 (1H, s, H7), 8.21 (1H, d, *J* 7.8 Hz, H8), 8.17 (1H, d, *J* 7.8 Hz, H11), 8.06 (1H, s, H12), 7.70 (1H, t, *J* 7.8 Hz, H10), 7.65 (1H, t, *J* 7.8 Hz, H9), 7.45–7.36 [5H, m, H2′-6′ (Ph)], 5.39 (1H, t, *J* 7.6 Hz, H5), 4.16 (1H, dd, *J* 10.2, 7.6 Hz, H4$_{exo}$), 3.32 (1H, d, *J* 18.0 Hz, H1$_{endo}$), 3.15 (1H, d, *J* 18.0 Hz, H1$_{exo}$), 3.01 (1H, dd, *J* 10.2, 7.6 Hz, H4$_{endo}$); ^{13}C NMR ($CDCl_3$) δ 173.3 (C2), 172.9 (C2), 143.5 (C12a), 139.7 [C1′, (Ph)], 136.3 (C11a), 134.5 (C7a), 130.3 (C8), 129.7 [C3′5′, (Ph)], 129.2 (C10), 128.9 (C11), 128.7 (C6a), 128.2 [C4′, (Ph)], 128.0 (C9), 125.4 (C7), 125.9 [C2′6′, (Ph)], 122.1 (C12), 90.7 (C12b), 67.1 (C4), 59.4 (C5), 39.0 (C1). Anal. Calcd for $C_{22}H_{17}N_3O_2$ (355.39) C, 74.35; H, 4.82; N, 11.82. Found: C, 74.21; H, 4.88; N, 11.91%.

*4.4.8. (R_p,5S)-(Z)-4,5-Dihydro-2-hydroxy-5-iso-propylpyrazolo[1,5-d]benzo[f][1,4]diazocin-7(6H)-one (**21a**).* Yield: 0.200 g, 37%; white solid, mp 244–248 °C; R_f (DCM/MeOH 20/1) 0.16; $[\alpha]_D^{25}$ −11.8 (*c* 0.6, DMSO); ν_{max} ~3400–2300, 1658, 1627, 1520 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.58 (1H, br s, OH), 7.94 (1H, d, *J* 9.5 Hz, NH), 7.49 (1H, t, *J* 7.3 Hz, H10), 7.45 (1H, t, *J* 7.3 Hz, H9), 7.34 (1H, d, *J* 7.3 Hz, H8), 7.27 (1H, d, *J* 7.3 Hz, H11), 5.58 (1H, s, H1), 4.06 (1H, dd, *J* 13.1, 4.6 Hz, H4$_{endo}$), 3.91 (1H, t, *J* 13.1 Hz, H4$_{exo}$), 3.24 (1H, m, H5), 1.77 [1H, m, C*H*(CH$_3$)$_2$], 0.88 [3H, d, *J* 6.8 Hz, CH(C*H*$_3$)(CH$_3$)], 0.76 [3H, d, *J* 6.8 Hz, CH(CH$_3$)(C*H*$_3$)]; ^{13}C NMR (DMSO-d_6) δ 171.9 (C7), 161.0 (C2), 142.7 (C11b), 136.2 (C7a), 130.6 (C9) and 130.5 (C10), 130.1 (C8), 129.1 (C11a), 127.8 (C8), 96.3 (C1), 57.3 (C5), 56.5 (C4), 31.5 [*C*H(CH$_3$)$_2$], 20.1 [CH(*C*H$_3$)(CH$_3$)], 19.9 [CH(CH$_3$)(*C*H$_3$)]; ^{15}N NMR (DMSO-d_6) δ 272 (N3), 185 (N3a), 128 (N6). Anal. Calcd for $C_{15}H_{17}N_3O_2$ (271.31) C, 66.40; H, 6.32; N, 15.49. Found: C, 66.37; H, 6.39; N, 15.56%.

*4.4.9. (R_p,5S)-(Z)-4,5-Dihydro-2-hydroxy-1-methyl-5-iso-propylpyrazolo[1,5-d]benzo[f][1,4]diazocin-7(6H)-one (**21b**).* Yield: 0.114 g, 20%; white solid, mp 230–232 °C; R_f (DCM/MeOH 20/1) 0.16; $[\alpha]_D^{25}$ −4.9 (*c* 0.5, DMSO); ν_{max} 3400–2300, 1660, 1638, 1525 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.58 (1H, br s, OH), 8.01 (1H, d, *J* 9.5 Hz, NH), 7.54 (1H, t, *J* 7.8 Hz, H10), 7.50 (1H, t, *J* 7.8 Hz, H9), 7.38 (1H, d, *J* 7.8 Hz, H8), 7.33 (1H, d, *J* 7.8 Hz, H11), 4.02 (1H, dd, *J* 13.2, 4.4 Hz, H4$_{endo}$), 3.85 (1H, t, *J* 13.2 Hz, H4$_{exo}$), 3.20 (1H, m, H5), 1.74 [1H, m, C*H*(CH$_3$)$_2$], 1.66 (3H, s 1-C*H*$_3$), 0.87 [3H, d, *J* 6.9 Hz, CH(C*H*$_3$)(CH$_3$)], 0.79 [3H, d, *J* 6.9 Hz, CH(CH$_3$)(C*H*$_3$)]; ^{13}C NMR (DMSO-d_6) δ 171.9 (C7), 159.7 (C2), 139.1 (C11b), 137.2 (C7a), 130.8 (C10), 130.3 (C9), 130.0 (C8), 128.5 (C11a), 127.7 (C11), 101.7 (C1), 57.7 (C5), 56.4 (C4), 31.7 [*C*H(CH$_3$)$_2$], 20.3 [CH(*C*H$_3$)(CH$_3$)], 19.8 [CH(CH$_3$)(*C*H$_3$)], 7.9 (1-*C*H$_3$); ^{15}N NMR (DMSO-d_6) δ 271 (N3), 183 (N3a), 127 (N6). Anal. Calcd for $C_{15}H_{17}N_3O_2$ (285.34) C, 67.35; H, 6.71; N, 14.73. Found: C, 67.49; H, 6.78; N, 14.62%.

*4.4.10. (R_p,5S)-(Z)-4,5-Dihydro-2-hydroxy-5-iso-propylpyrazolo[1,5-d]naphtho[2,3-f][1,4]diazocin-7(6H)-one (**22a**).* Yield: 0.244 g, 38% (from **13a**); 0.514 g, 86% (from **13a***); white solid, mp 176–179 °C; R_f (DCM/MeOH 20/1) 0.12; $[\alpha]_D^{25}$ −60.7 (*c* 0.8, DMSO); ν_{max} ~3400–2500, 1650 (broad), 1640, 1530 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.90 (1H, br s, OH), 8.10 (1H, d, *J* 9.8 Hz, NH), 8.04 (1H, m, H9), 8.00 (1H, m, H12), 7.97 (1H, s, H8), 7.94 (1H, s, H13), 7.64–7.60 (2H, m, H10,11), 5.59 (1H, s, H1), 4.04 (1H, dd, *J* 13.2, 4.7 Hz, H4$_{endo}$), 3.90 (1H, t, *J* 13.2 Hz, H4$_{exo}$), 3.24 (1H, m, H5), 1.75 [1H, m, C*H*(CH$_3$)$_2$], 0.87 [3H, d, *J* 6.9 Hz, CH(C*H*$_3$)(CH$_3$)], 0.78 [3H, d, *J* 6.9 Hz, CH(CH$_3$)(C*H*$_3$)]; ^{13}C NMR (DMSO-d_6) δ 171.6 (C7), 162.2 (C2), 142.4 (C13b), 134.6 (C7a), 133.7 (12a), 133.3 (C8a), 129.6 (C8), 128.9 (two coalesced lines, C9,12), 128.4 (C11), 128.1 (C10), 127.4 (C13), 127.1 (C13a), 96.8 (C1), 57.2 (C5), 56.5 (C4), 31.7 [*C*H(CH$_3$)$_2$], 20.1 [CH(*C*H$_3$)(CH$_3$)], 19.8 [CH(CH$_3$)(*C*H$_3$)]; ^{15}N NMR (DMSO-d_6) δ 274 (N3), 185 (N3a), 127 (N6). Anal. Calcd for $C_{19}H_{19}N_3O_2$ (321.37) C, 71.01; H, 5.96; N, 13.08. Found: C, 70.90; H, 6.04; N, 13.02%.

*4.4.11. (R_p,5S)-(Z)-4,5-Dihydro-2-hydroxy-1-methyl-5-iso-propylpyrazolo[1,5-d]naphtho[2,3-f][1,4]diazocin-7(6H)-one (**22b**).* Yield: 0.244 g, 38%; white solid, mp 188–190 °C; R_f (DCM/MeOH 20/1) 0.19; $[\alpha]_D^{25}$ −31.0 (*c* 0.6, DMSO); ν_{max} ~3500–2500, 1652 (broad), 1632, 1539 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.70 (1H, br s, OH), 8.06 (1H, d, *J* 9.5 Hz, NH), 8.06–8.02 (2H, m, H9,12), 7.99 (1H, s, H8), 7.87 (1H, s, H13), 7.64–7.60 (2H, m, H10,11), 4.02 (1H, dd, *J* 13.0, 4.4 Hz, H4$_{endo}$), 3.85 (1H, t, *J* 13.0 Hz, H4$_{exo}$), 3.21 (1H, m, H5), 1.74 [1H, m, C*H*(CH$_3$)$_2$], 1.66 (3H, s 1-C*H*$_3$), 0.87 [3H, d, *J* 6.9 Hz, CH(C*H*$_3$)(CH$_3$)], 0.79 [3H, d, *J* 6.9 Hz, CH(CH$_3$)(C*H*$_3$)]; ^{13}C NMR (DMSO-d_6) δ 171.8 (C7), 160.2 (C2), 139.0 (C13b), 135.4 (C7a), 133.6 (12a), 133.2 (C8a), 130.3 (C8), 128.9 (two coalesced lines, C9,12), 128.3 (C10), 128.2 (C11), 127.3 (C13), 126.3 (C13a), 102.2 (C1), 57.5 (C5), 56.5 (C4), 31.5 [*C*H(CH$_3$)$_2$], 20.3 [CH(*C*H$_3$)(CH$_3$)], 19.8 [CH(CH$_3$)(*C*H$_3$)], 8.1 (1-*C*H$_3$); ^{15}N NMR (DMSO-d_6) 272 (N3), 182 (N3a), 127 (N6). Anal. Calcd for $C_{20}H_{21}N_3O_2$ (335.40) C, 71.62; H, 6.31; N, 12.53. Found: C, 71.58; H, 6.37; N, 12.61%.

*4.4.12. (R_p,5S)-(Z)-4,5-Dihydro-2-hydroxy-5-phenylpyrazolo[1,5-d]benzo[f][1,4]diazocin-7(6H)-one (**23a**).* Yield: 0.171 g, 28%; white solid, mp 222–225 °C; R_f (DCM/MeOH 20/1) 0.16; $[\alpha]_D^{25}$ +52.7 (*c* 0.9, DMSO); ν_{max} 3325, ~3300–2300, 1662, 1607, 1528 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.80 (1H, br s, OH), 8.24 (1H, d, *J* 10.5 Hz, NH), 7.54 (1H, t, *J* 7.8 Hz, H10), 7.50 (1H, t, *J* 7.8 Hz, H9), 7.42 [2H, d, *J* 7.6 Hz, H2′,6′ (Ph)], 7.38 (1H, d, *J* 7.8 Hz, H8), 7.36–7.32 [3H, m, H3′,5′ (Ph) and

H11], 7.29 [1H, t, *J* 7.6 Hz, H4′ (Ph)], 5.69 (1H, s, H1), 4.93 (1H, ddd, *J* 13.2, 10.5, 4.9 Hz, H5), 4.33 (1H, dd, *J* 13.2, 4.9 Hz, $H4_{endo}$), 4.24 (1H, t, *J* 13.0 Hz, $H4_{exo}$); ^{13}C NMR (DMSO-d_6) δ 171.8 (C7), 160.2 (C2), 142.1 [C1′,(Ph)], 139.1 (C11b), 137.2 (C7a), 130.8 (C10), 130.3 (C9), 130.0 (C8), 129.7 [C3′5′, (Ph)], 128.5128.3 [C4′, (Ph)], (C11a), 127.7 (C11), 126.0 [C2′6′, (Ph)], 101.7 (C1), 58.2 (C5), 52.5 (C4); ^{15}N NMR (DMSO-d_6) 275 (N3), 184 (N3a), 130 (N6). Anal. Calcd for $C_{18}H_{15}N_3O_2$ (305.33) C, 70.81; H, 4.95; N, 13.76. Found: C, 70.94; H, 5.04; N, 13.72%.

*4.4.13. (R_p,5S)-(Z)-4,5-Dihydro-2-hydroxy-5-phenylpyrazolo[1,5-d]naphtho[2,3-f][1,4]diazocin-7(6H)-one (**24a**).* Yield: 0.121 g, 17% (from **15a**); 0.583 g, 81% (from **15a***); pale yellowish solid, mp 300–303 °C; R_f (DCM/MeOH 20/1) 0.12; $[\alpha]_D^{25}$ +73.8 (*c* 0.6, DMSO); ν_{max} 3305, ~3150–2300, 1659 (broad), 1610, 1533 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.89 (1H, br s, OH), 8.22 (1H, d, *J* 10.7 Hz, NH), 8.09–8.06 (2H, m, H9,12), 8.05 (1H, s, H8), 8.04 (1H, s, H13), 7.66–7.60 (2H, m, H10,11), 7.40 [2H, d, *J* 7.7 Hz, H2′,6′ (Ph)], 7.33 [2H, t, *J* 7.7 Hz, H3′,5′ (Ph)], 7.29 [1H, t, *J* 7.7 Hz, H4′ (Ph)], 5.70 (1H, s, H1), 4.94 (1H, ddd, *J* 13.0, 10.7, 4.9 Hz, H5), 4.33 (1H, dd, *J* 13.0, 4.9 Hz, $H4_{endo}$), 4.24 (1H, t, *J* 13.0 Hz, $H4_{exo}$); ^{13}C NMR (DMSO-d_6) δ 171.6 (C7), 160.0 (C2), 142.2 [C1′,(Ph)], 139.1 (C13b), 135.2 (C7a), 133.6 (12a), 133.4 (C8a), 130.4 (C8), 129.6 [C3′5′, (Ph)], 129.0 (C9), 128.8 (C12), 128.5 (C10), 128.3 [C4′, (Ph)], 128.0 (11), 127.3 (C13), 126.5 (C13a), 125.9 [C2′6′, (Ph)], 101.8 (C1), 58.3 (C5), 52.5 (C4); ^{15}N NMR (DMSO-d_6) 273 (N3), 183 (N3a), 129 (N6). Anal. Calcd for $C_{22}H_{17}N_3O_2$ (355.39) C, 74.35; H, 4.82; N, 11.82. Found: C, 74.28; H, 4.88; N, 11.93%.

4.4.14. (R_p^*,5S)-(Z)-4,5-Dihydro-2-hydroxy-5-ethylpyrazolo[1,5-d]naphtho[2,3-f][1,4]diazocin-7(6H)-one (**25a**).* Yield: 0.381 g, 62% (from **16a**); 0.479 g, 78% (from **16a***); white solid, mp 243–246 °C; R_f (DCM/MeOH 20/1) 0.16; ν_{max} 3305, ~3150–2300, 1665, 1610, 1531 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.94 (1H, br s, OH), 8.15 (1H, d, *J* 9.5 Hz, NH), 8.04 (1H, m, H9), 8.02 (1H, m, H12), 7.97 (1H, s, H8), 7.93 (1H, s, H13), 7.64–7.60 (2H, m, H10,11), 5.60 (1H, s, H1), 4.00 (1H, dd, *J* 12.3, 3.9 Hz, $4H_{endo}$), 3.79 (1H, t, *J* 12.3, $4H_{exo}$), 3.46 (1H, m, 5H), 1.46 (2H, quint, *J* 7.0 Hz, CH_2CH_3), 0.80 (3H, t, *J* 7.0 Hz, CH_2CH_3); ^{13}C NMR (DMSO–d_6) δ 171.7 (C7), 162.0 (C2), 128.9 (two coalesced lines, C9,12), 128.4 (C11), 128.1 (C10), 127.4 (C13), 127.3 (C13a), 96.5 (C1), 58.0 (C4), 53.5 (C5), 25.8 (CH_2CH_3), 11.4 (CH_2CH_3); ^{15}N NMR (DMSO-d_6) 273 (N3), 183 (N3a), 127 (N6). Anal. Calcd for $C_{18}H_{17}N_3O_2$ (307.35) C, 70.34; H, 5.58; N, 13.67. Found: C, 70.31; H, 5.65; N, 13.77%.

4.4.15. (R_p^*,5S)-(Z)-4,5-Dihydro-2-hydroxy-5-ethyl-1-methylpyrazolo[1,5-d]naphtho[2,3-f][1,4]diazocin-7(6H)-one (**25b**).* Yield: 0.373 g, 58%; white solid, mp 258–261 °C; R_f (DCM/MeOH 20/1) 0.20; ν_{max} 3290, ~3250–2300, 1660, 1612, 1538 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.72 (1H, br s, OH), 8.10 (1H, d, *J* 9.7 Hz, NH), 8.06–8.01 (2H, m, H9,12), 7.97 (1H, s, H8), 7.88 (1H, s, H13), 7.64–7.60 (2H, m, H10,11), 3.97 (1H, dd, *J* 12.0, 4.0 Hz, $H4_{endo}$), 3.76 (1H, t, *J* 12.0 Hz, $H4_{exo}$), 3.37 (1H, m, H5), 1.62 (3H, s, 1-CH_3), 1.42 (2H, quint, *J* 7.0 Hz, CH_2CH_3), 0.78 (3H, t, *J* 7.0 Hz, CH_2CH_3); ^{13}C NMR (DMSO-d_6) δ 171.8 (C7), 159.9 (C2), 139.2 (C13b), 135.6 (C7a), 134.0 (12a), 133.4 (C8a), 130.3 (C8), 128.9 (two coalesced lines, C9,12), 128.5 (C10), 128.2 (C11), 127.3 (C13), 126.2 (C13a), 102.4 (C1), 57.8 (C4), 53.6 (C5), 25.4 (CH_2CH_3), 11.5 (CH_2CH_3), 8.0 (1-CH_3); ^{15}N NMR (DMSO-d_6) 270 (N3), 182 (N3a), 131 (N6). Anal. Calcd for $C_{19}H_{19}N_3O_2$ (321.37) C, 71.01; H, 5.96; N, 13.08. Found: C, 71.11; H, 6.07; N, 12.99%.

*4.4.16. 2-{(S)-2-[(3S,9bS)-2,3,5,9b-Tetrahydro-1-propanoylamino-3-iso-propyl-5-oxo-1H-imidazo[2,1-a]isoindol-9b-yl]propanoyl}-1(propan-2-ylidene)hydrazine (**26b**).* Yield: 0.099 g, 12%; white solid, mp 108–111 °C; R_f (DCM/MeOH 20/1) 0.53; $[\alpha]_D^{25}$ −44.8 (*c* 1.3, DMSO) ν_{max} 3202, 3047, 1667 (broad), 1533 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.75 [1H, s, (=N–NH)], 9.20 (1H, s, 3-NH), 7.61 (1H, m, H7), 7.57–7.49 (2H, m, H8,9), 7.18 (1H, m, H10), 4.07 (1H, dd, *J* 13.9, 8.5 Hz, $H4_{exo}$), 3.83 (1H, m, H5), 3.64 (1H, dd, *J* 13.9, 7.6 Hz, $H4_{endo}$), 3.30 (1H, quartet, *J* 7.0 Hz, H1), 2.02 [3H, s, (CH_3)(CH_3)C=N–NH (‘*E*’ relative to NH)], 1.96 [3H, s, (CH_3)(CH_3)C=N–NH (‘*Z*’ relative to NH)], 1.69 [1H, m, $CH(CH_3)_2$], 1.55 (1H, dquartet, *J* 14.1, 7.6 Hz, $COCH_AH_BCH_3$), 1.43 (1H, dquartet, *J* 14.1, 7.6 Hz, $COCH_AH_BCH_3$), 1.11 [3H, d, *J* 7.6 Hz, CH(CH_3)(CH_3)], 0.87 [3H, d, *J* 7.6 Hz, CH(CH_3)(CH_3)], 0.67 (3H, d, *J* 7.0 Hz, 1-CH_3), 0.37 (3H, t, *J* 7.6 Hz, $COCH_2CH_3$); ^{13}C NMR (DMSO-d_6) δ 171.7 ($COCH_2CH_3$), 171.0 (C6), 167.1 (C2), 158.4 [$(CH_3)_2C$=N–NH], 141.3 (C10a), 135.3 (C6a), 132.7 (C9), 131.0 (C8), 124.6 (C10), 123.6 (C7), 97.2 (C10b), 63.2 (C4), 60.1 (C5), 43.0 (C1), 34.4 [$CH(CH_3)_2$], 27.2 ($COCH_2CH_3$), 26.0, [(CH_3)(CH_3)C=N–NH (‘*E*’ relative to NH)], 22.5 [CH(CH_3)(CH_3)], 19.9 [CH(CH_3)(CH_3)], 18.8, [(CH_3)(CH_3)C=N–NH (‘*Z*’ relative to NH)], 11.6 (1-CH_3), 10.6 ($COCH_2CH_3$); ^{15}N NMR (DMSO-d_6) δ 308 [(=*N*–NH)], 171 [(=N–*N*H)], 153 (N3), 125 (N5a), 99 (N3a). Anal. Calcd for $C_{22}H_{31}N_5O_3$ (413.51) C, 63.90; H, 7.56; N, 16.94. Found: C, 64.02; H, 7.52; N, 16.87%.

4.5. General procedure for the ring enlargement of tetra- and pentacycles 5c, 6a–c, 12a,b, 13a,b, 14a and 15a effected by $NaHCO_3$ (method B)

A mixture of the appropriate precursor (1 mmol) and 10% $NaHCO_3$ (10 mL) was heated at reflux for 3 h. The resultant yellow solution was cooled and its pH was adjusted to 7–8 by concd HCl. After standing for 1 h in the refrigerator the precipitated crystals were collected, washed with water and dried in a vacuum desiccator over P_2O_5. Yield: 0.151 g, 53% for **2c**; 0.178 g, 58% for **7a**; 0.167 g, 52% for **7b**; 0.164 g, 49% for **7c**; 0.149 g, 55% for **21a**; 0.140 g, 49% for **21b**; 0.161 g, 50% for **22a**; 0.164 g, 49% for **22b**; 0.159 g, 52% for **23a**; 0.114 g, 32% for **24a**. Analytical samples were obtained by recrystallization from EtOH. Within experimental error spectroscopic and analytical data proved to be identical listed in the paragraphs above.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.02.034. These data include MOL files and InChiKeys of the most important compounds described in this article.

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