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Synthesis and transformations of new dihydro-β-campholenolactone derivatives

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Abstract—The reaction of xenon difluoride with enamino lactone **3** furnished the new α-fluoro aldehyde **7**, whereas reaction of **3** with anhydrous HF led to racemic dihydro-β-campholenolactone **6**. Acid-catalysed rearrangement of α-ethylidenelactone **4** proceeded with retention of configuration to give β-campholenolactone **8**. Nitrosation of the novel bicyclic enamino lactone **6** afforded the corresponding oxime **9**, while acid-catalysed treatment with primary amines, 2-methyl-1*H*-indole, potassium cyanide and hydrazine hydrochloride, furnished the dimethylamine substitution products **11**–**13** and the 'ring switched' product **14**. The structures were determined by 2D NMR techniques, NOESY spectroscopy and X-ray diffraction.

1. Introduction

(+)-Camphor **1** and its derivatives are among the most frequently employed as types of chiral pool starting materials, building blocks, ligands in various asymmetric reagents and/or catalysts, resolving agents and as shift reagents in NMR spectroscopy.[1–4] For example, various fluorinated 3-hydroxymethylidenecamphor derivatives are the most common ligands in chiral lanthanide shift reagents.[5–8]

Recently, a series of alkyl 2-substituted 3-(dimethylamino)propenoates and related enaminones have been prepared and used as versatile reagents in the synthesis of various heterocyclic systems and natural product analogues,[9–14] as well as in the combinatorial synthesis of dehydroalanines and fused pyridones, pyrimidones and pyranones.[15–18] In this context, chiral enaminones, derived from α-amino acids, have been employed in the synthesis of β-heteroarylalanines and related functionalised heterocycles with an α-amino acid, dipeptide, β-amino alcohol, α-hydroxy acid and 1,2-diol structural element.[10–13,19–22] Our studies on chiral pool derived enaminones have recently been extended to the preparation and synthetic applications of (+)-camphor derived enaminones.[23–30] Aiming at utilisation of terpene-functionalised enaminones in preparation of novel fluorinated (+)-camphor (**1**) analogues, it seemed reasonable to us to study the reactions of enamino camphorlactone **3** with fluorine containing reagents and/or solvents. Herein, we now report the results of this study, the preparation of α-formyl-α-fluoro-1,2-campholide **7** and dihydro-β-campholenolactone derivatives **6** and **8**–**14**.

2. Results and discussion

Starting compounds **3**[24] and **4**[26] were prepared from (1*R*)-(+)-camphor **1** according to the literature procedures. Compounds **3** and **4** were then subjected to various fluorine containing reagents and/or solvents. Surprisingly, dissolving and stirring of compound **3** in anhydrous hydrofluoric acid furnished racemic *rel*-(3a*R*,6a*S*,3*E*)-3-[(dimethylamino)methylidene]-6,6,6a-trimethylhexahydro-2*H*-cyclopenta[*b*]furan-2-one **6** in 70% yield. All the analyses for compound **6** (^{1}H NMR, IR, CHN and MS) and the fact that enaminones exhibit configurational instability[24] initially led us to believe that the isolated compound **6** could be the *Z*-isomer of the starting *E*-enaminone **3**, formed via acid-catalysed *E*/*Z* isomerisation of **3**. Only the X-ray structural analysis disclosed the structure of **6**, which

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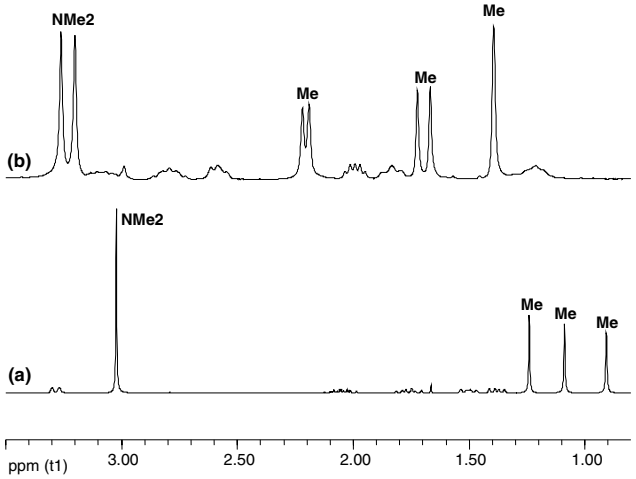
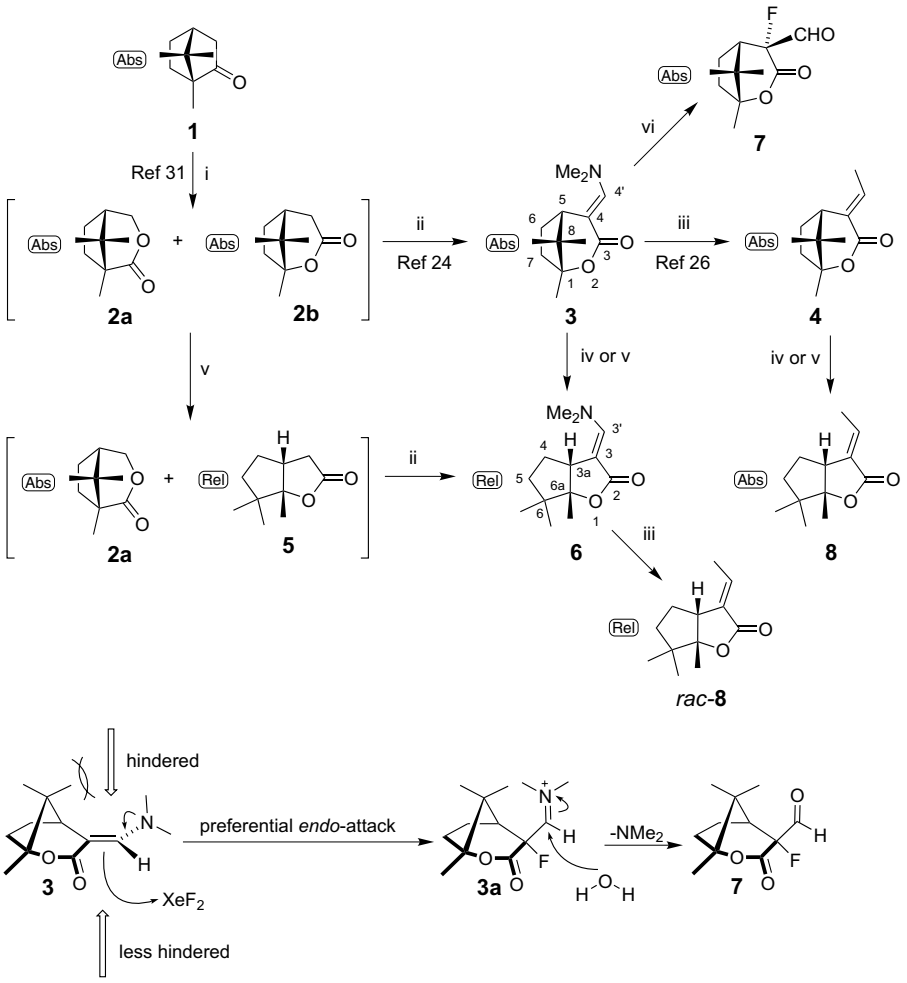


Figure 1. Partial (0.8–3.5 δ ppm) ^{1}H NMR spectra of (a) compound **6** in $CDCl_3$ and (b) a mixture of 10 mg of **6** and 30 mg of tris[3-(heptafluoropropylhydroxymethylene)-D-camphorato] europium(III) in $CDCl_3$.

turned out to be the acid-catalysed rearrangement product of **3**, the *rel*-(3a*R*,6a*S*,3*E*)-3-[(dimethylamino)methylidene]-6,6,6a-trimethylhexahydro-2*H*-cyclopenta[*b*]furan-2-one **6** (Fig. 1). After a literature search, we found that acid-catalysed rearrangement (H_2SO_4–AcOH) of structurally similar 1,2-campholide **2b** gave racemic dihydro-β-campholenolactone **5**.[31] This prompted us to repeat the rearrangement of **3** in a mixture of H_2SO_4 and AcOH due to the obvious reasons of inexpensive and easy to handle reagents in comparison to HF. Using this method, the rearrangement product **6** was obtained in 43% yield, again as the racemate. The lower yields of product **6** in this reaction, when compared to the reaction carried out in HF, could be ascribed to the loss of product **6** during isolation, where part of **6** was probably hydrolysed into a hydroxymethylidene compound. The initial TLC-screening of the reaction mixture in H_2SO_4–AcOH showed a total conversion of **3** into **6**. Finally, a more convenient synthetic modification was used to prepare **6** on a larger scale in two steps from **2b**. A mixture of Baeyer–Villiger oxidation products **2a** and **2b** (**2a**:**2b** ≈ 30:70) was subjected to the rearrangement conditions (H_2SO_4–AcOH) described in the literature[31] to furnish campholenolactone **5** and unreacted lactone **2a** in an approximate ratio of 30:70, with a total conversion of **2b** into **5**. No attempts were made to separate **2a** and **5**. Instead, the mixture of **2a** and **5** was reacted with bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent) to furnish, after purification, racemic enaminone **6** in 83% yield. In contrast to enaminone **3**, α-ethylidene compound **4** in HF underwent a stereoselective acid-catalysed rearrangement to yield the non-racemic (3a*R*,6a*S*,3*E*)-3-ethylidene-6,6,6a-trimethylhexahydro-2*H*-cyclopenta[*b*]furan-2-one **8** as a single enantiomer in 79% yield. A repeated rearrangement of **4** in a mixture of H_2SO_4 and AcOH furnished enantiopure **8** in 87% yield. Finally, racemic *rel*-(3a*R*,6a*S*,3*E*)-3-ethylidene-6,6,6a-trimethylhexahydro-2*H*-cyclopenta[*b*]furan-2-one *rac*-**8** was prepared in 23% yield from racemic enaminone *rac*-**6** and methylmagnesium bromide, via substitution of the dimethylamino group according to a literature procedure.[26] Much to our disappointment, the reactions of **3** and **4** with excess XeF_2 ($\geqslant$4 equiv), with XeF_2–BF_3 in methanol and with F_2 in HF gave complex mixtures of products that could not be separated and identified. On the other hand, the reaction of **3** with XeF_2 in acetonitrile with a molar ratio of 1:1.24, respectively, furnished α-fluoro aldehyde **7** as a single diastereoisomer in 20% yield. The formation of **7** was not unexpected, since similar enol acetates and silyl enol ethers also gave α-fluoro carbonyl products upon reaction with XeF_2.[32–39] The formation of **7** could be explained by initial attack of the electrophilic XeF_2 from the less hindered *endo*-face of the nucleophilic enamine C=C double bond of **3**[1,7,40–44] to form the intermediate **3a**, which was subsequently hydrolysed with water, present in the solvents used for product purification, to give the final α-fluoro aldehyde **7** (Scheme 1).

The reactivity of the new enaminone reagent **6** was determined in a nitrosation reaction and in reactions with *N*- and *C*-nucleophiles. Generally, the reactions of enaminones under nitrosating conditions ($NaNO_2$/HCl) lead to the formation of oximes.[9–12,19,45–47] Accordingly, the nitrosation of **6** with aqueous sodium nitrite in the presence of hydrochloric acid gave the expected oxime, (3a*R*,6a*S*,3*E*)-3-(hydroxyimino)-6,6,6a-trimethylhexahydro-2*H*-cyclopenta[*b*]furan-2-one **9**, in 93% yield. The reactions of **6** with nucleophiles were all acid-catalysed. In all cases, mononucleophiles only gave dimethylamine substitution products. Thus, treatment of **6** with primary amines **10a**–**k** in anhydrous ethanol in the presence of an equimolar amount of hydrochloric or sulfuric acid at room temperature or at reflux afforded the corresponding dimethylamine substitution products **11**/**11′** in 20–67% yield. Compounds **11a**–**d**,**f**–**i**,**k** were obtained as single isomers, whilst compounds **11**/**11′e**,**j** were isolated as mixtures of the major (*E*)-isomers **11e**,**j** and the minor (*Z*)-isomers **11′e**,**j**. In the same manner, the reaction of **6** with 2-methyl-1*H*-indole and KCN in acetic acid furnished the corresponding substitution products **12** and **13** in 86% and 63% yield, respectively. Finally, the reaction of **6** with hydrazine hydrochloride in ethanol at reflux afforded *rel*-4-[(1*S*,2*R*)-2-hydroxy-2,3,3-trimethylcyclopentyl]-1*H*-pyrazol-3-ol **14** in 95% yield. The formation of the 'ring switched' product **14** was expected and was also in agreement with the typical reactivity of related enamino lactones and lactams towards ambident nucleophiles (Scheme 2 and Table 1).[10–12,19,20,25]

Currently, we are unable to explain the stereochemical outcome of the acid-catalysed rearrangement of enantiopure compounds **3** and **4** into campholenolactones **6** (racemate) and **8** (single enantiomer), respectively. The proposed mechanism is analogous to that found in the literature[48] for the rearrangement of 1,2-campholide **2b** into dihydro-β-campholenolactone **5**. In the case of compound **8**, protonation gives the O-protonated species **15a**, which undergoes ring-opening to give carbocation **16a**. Migration of one methyl group from position 8 to position 1 gives the rearranged cation **17a**, followed by ring closure to furnish optically active compound **8**. Similarly, enaminone **3** can rearrange into the corresponding cation **17b**, which can isomerise into ammonium cation **18b**. Equilibration between enantiopure **17b** and achiral **18b** results in the



Scheme 1. Reagents and conditions: (i) AcOOH, AcOH, rt; (ii) *t*-BuOCH(NMe_2)$_2$, decalin, reflux; (iii) MeMgBr (6 or 21 equiv), THF, −78 °C to rt; (iv) HF, −196 °C→rt; (v) AcOH, H_2SO_4, rt; (vi) MeCN, XeF_2, −196 °C→rt.

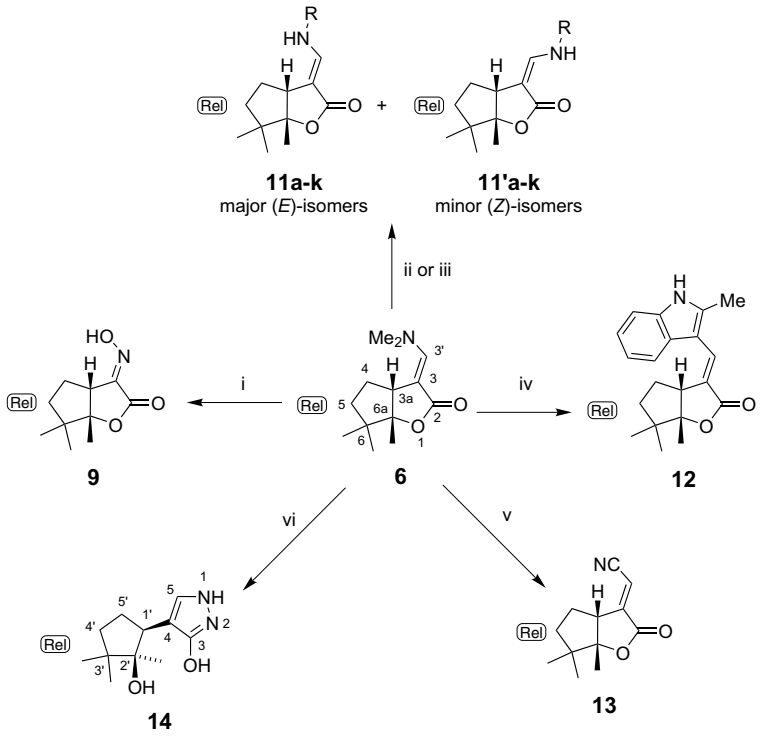
racemisation of **17b** and, consequently, the final lactonisation (ring closure) of *rac*-**17b** leads to racemic compound **6** (Scheme 3).

3. Structure determination

The structures of dihydro-β-campholenolactone derivatives **6** and **8**, α-fluoro aldehyde **7**, oxime **9**, dimethylamine substitution products **11/11′a**–**k**, **12** and **13** and 'ring switched' product **14** were determined by spectroscopic methods (IR, ^{1}H and ^{13}C NMR, 2D NMR, NOESY spectroscopy, MS) as well as elemental analyses for C, H and N. Compounds **6**–**9**, **11a**–**d**,**f**–**i**,**k** and **12**–**14** were prepared in isomerically pure form. Compounds **11/11′e** and **11/11′j** were characterised as mixtures of the major (*E*)-isomers **11e**,**j** and the minor (*Z*)-isomers **11e**,**j**. Compound **7** was prepared as a single enantiomer, compound **8** as a single enantiomer or racemic compound, whereas all the other new compounds **9**, **11**–**14** were obtained as racemic compounds. Compounds **9**, **11c**,**g**, **12** and **13** were not prepared in analytically pure forms. The identities of **8**, **9**, **11c**,**g**, **12** and **13** were confirmed by ^{13}C NMR and EI-HRMS.

Compound **6** was always isolated as a racemate that showed no rotation of polarised light. The addition of an enantiopure shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-D-camphorato] europium(III), to compound **6** caused splitting of two out of the three methyl groups and splitting of the NMe_2 group in a 1:1 ratio in ^{1}H NMR spectra when recorded in $CDCl_3$ (Fig. 1). The same observations were made for optically inactive compound *rac*-**8**, prepared from **6** and MeMgBr (Fig. 2). On the other hand, compound **8**, obtained upon acid-catalysed rearrangement of **4**, showed a strong rotation of polarised light (see Experimental, Section 5.4). The ee of **8** was then determined by ^{1}H NMR in the presence of enantiopure shift reagent. The ^{1}H NMR spectrum of **8** in the presence of tris[3-(heptafluoropropylhydroxymethylene)-D-camphorato] europium(III) did not exhibit any splitting of signals for the methyl groups, therefore confirming compound **8** to be a single enantiomer (Fig. 3).

The configuration around the exocyclic C=C double bond in compounds **11d**, **11g**, **12** and **13** was determined by NMR on the basis of long-range coupling constants ($^5J_{C-H}$) between the methylidene proton (*H*–C(3′)) and



Scheme 2. Reagents and conditions: (i) $NaNO_2$, HCl, H_2O, 0 °C to rt, then AcOH; (ii) R–NH_2 × HCl (**10a**,**b**, 1 equiv), EtOH, rt; (iii) R–NH_2 (**10c**–**k**, 1 equiv), EtOH, H_2SO_4 (1 equiv), reflux, then rt; (iv) 2-methyl-1*H*-indole, AcOH, reflux; (v) KCN, AcOH, rt; (vi) NH_2NH_2 × HCl, EtOH, reflux.

Table 1. Selected experimental data for methylidene compounds **11**/**11′**, **12** and **13**

Compound	R	Yield [%]	*E*:*Z*[a]
11a	Phenyl	57	100:0
11b	4-Methylphenyl	31	100:0
11c	3-Methylphenyl	32	100:0
11d	4-Methoxyphenyl	62	100:0
11e, **11′e**	3-Methoxyphenyl	67	93:7
11f	4-Bromophenyl	63	100:0
11g	3-Bromophenyl	51	100:0
11h	4-Nitrophenyl	43	100:0
11i	3-Nitrophenyl	23	100:0
11j, **11′j**	2-Nitrophenyl	20	63:37
11k	1-Naphthyl	60	100:0
12	—	86	100:0
13	—	63	100:0

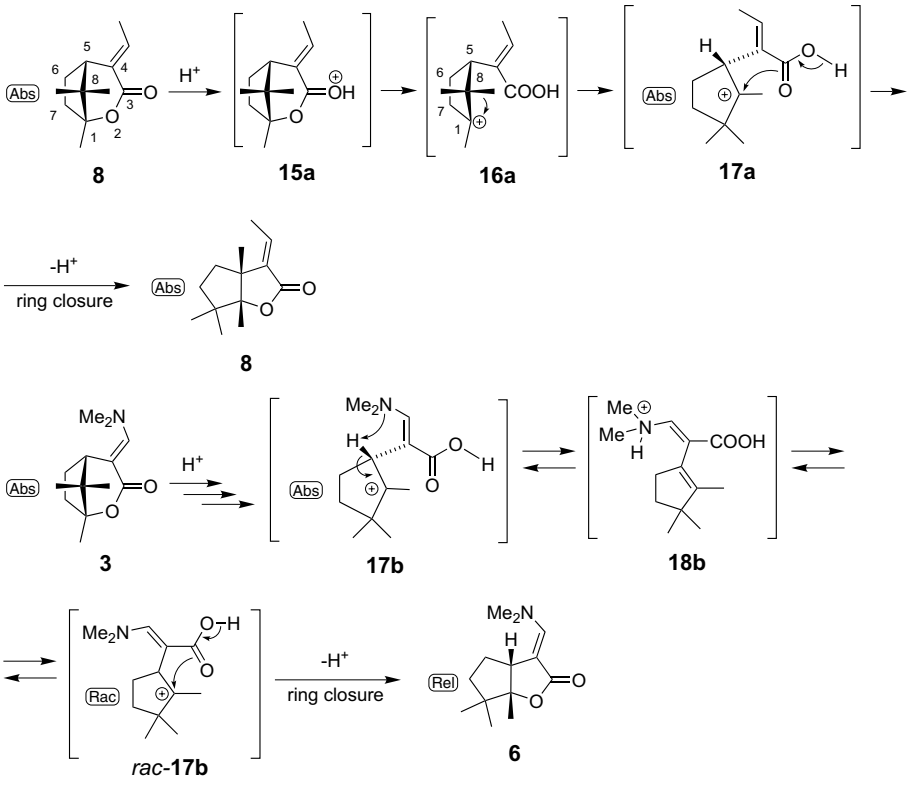
[a] Determined by ^{1}H NMR.

the carbonyl carbon atom (O=*C*(2)), measured from the antiphase splitting of cross peaks in the HMBC spectrum. Generally, the magnitude of coupling constant, $^3J_{C–H}$, for nuclei with *cis*-configuration around the C=C double bond is smaller (2–6 Hz) than that for *trans*-oriented nuclei (8–12 Hz).[10–12,24,26,28,49–59] The magnitude of the coupling constant in compounds **11d** ($^3J_{C–H} = 4.0$ Hz), **11g** ($^3J_{C–H} = 4.3$ Hz) and **13** ($^3J_{C–H} = 5.8$ Hz) indicated an (*E*)-configuration around the exocyclic C=C double bond (Fig. 4). The magnitude of the coupling constant in compound **12** ($^3J_{C–H} = 7.6$ Hz) could not be used as a reliable criterion for the unambiguous determination of configuration around the C=C double bond. However, the identical magnitude of the coupling constant in a closely related (1*R*,5*S*)-[(*E*)-(2-methyl-1*H*-indol-3-yl)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one ($^3J_{C–H} = 7.6$ Hz), where the *trans*-configuration was confirmed by X-ray diffraction,[26] strongly indicates the *trans*-configuration in compound **12** (Fig. 4).

The (*E*)-configuration around the exocyclic C=C double bond in the major isomers **11a**–**k** was determined by NOESY spectroscopy, on the basis of NOE between N–*H* and *H*–C(3a). On the other hand, NOE between *H*–C(3′) and *H*–C(3a) indicated a (*Z*)-configuration in the minor isomer **11′j** (Fig. 4). Such as in the case of structurally related α-alkylidene-1,2-campholides[24,26,28] and tetramic acids,[60] the *E*/*Z*-configuration of isomeric compounds **11** and **11′** was correlated with typical chemical shifts for the *H*–C(3′), N*H* and *H*–C(3a) protons and vicinal coupling constants, $J_{CH–NH}$ and $J_{H(3a)–H(4)}$. Unfortunately, the dependence of the chemical shifts and coupling constant magnitudes on the configurations in compounds **11** and **11′** was less pronounced than in the previously reported analogues. The lack of ^{1}H NMR data for the minor isomers **11′** (only two examples) makes this method quite unreliable for the determination of (*E*/*Z*)-configuration (Table 2). The structures of compounds **6**, **7** and **8** were determined by X-ray diffraction (Figs. 5–7).

4. Conclusion

In conclusion, enaminone **3** and α,β-unsaturated lactone **4** are quite sensitive towards fluorinating agents, such as



Scheme 3.

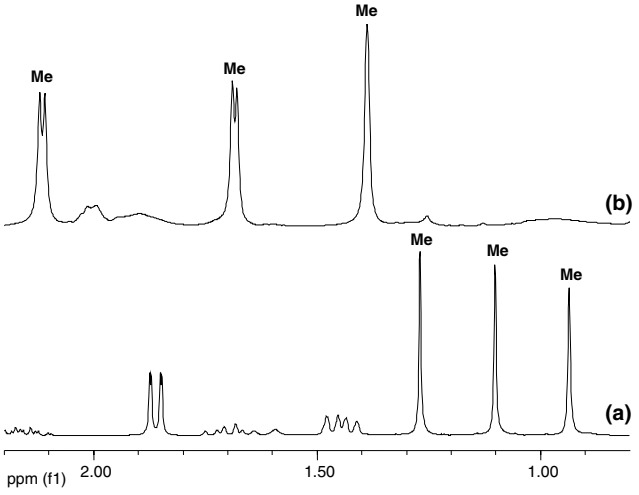


Figure 2. Partial (0.8–2.2 δ ppm) ^{1}H NMR spectra of (a) *rac*-**8** in $CDCl_3$ and (b) a mixture of 10 mg of *rac*-**8** and 30 mg of tris[3-(heptafluoropropylhydroxymethylene)-D-camphorato] europium(III) in $CDCl_3$.

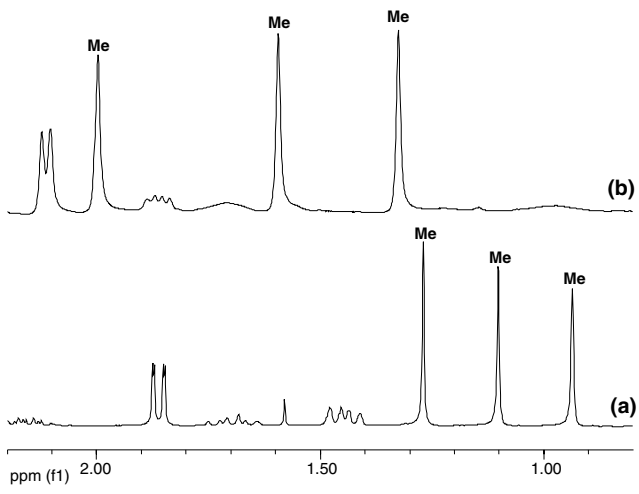


Figure 3. Partial (0.8–2.2 δ ppm) ^{1}H NMR spectra of (a) compound **8** in $CDCl_3$ and (b) a mixture of 10 mg of **8** and 30 mg of tris[3-(heptafluoropropylhydroxymethylene)-D-camphorato] europium(III) in $CDCl_3$.

XeF_2, XeF_2–BF_3–MeOH and F_2–HF. Most of the experiments resulted in complex mixtures of products that could not be separated or identified. Nevertheless, the reaction of enaminone **3** with XeF_2 in acetonitrile furnished a novel α-fluoro-α-formyl-1,2-campholide **7**, isolated as a single stereoisomer in moderate yield. On the other hand, treatment of **3** and **4** with anhydrous HF gave dihydro-β-campholenolactone derivatives **6** and **8**, respectively; the former as a racemate and the latter as a single stereoisomer. Unfortunately, we do not have a firm mechanistic explanation for the different stereochemical outcomes of these rearrangements. At present, this problem exceeds the scope of this research and needs further elaboration in the future. Identical products **6** and **8** were also obtained from **3** and **4**, respectively, upon treatment in a mixture of acetic and sulfuric acid instead of anhydrous HF. Consequently, a convenient large-scale synthesis of **6** has been established, proceeding in three steps from (+)-camphor (**1**) via Bae-

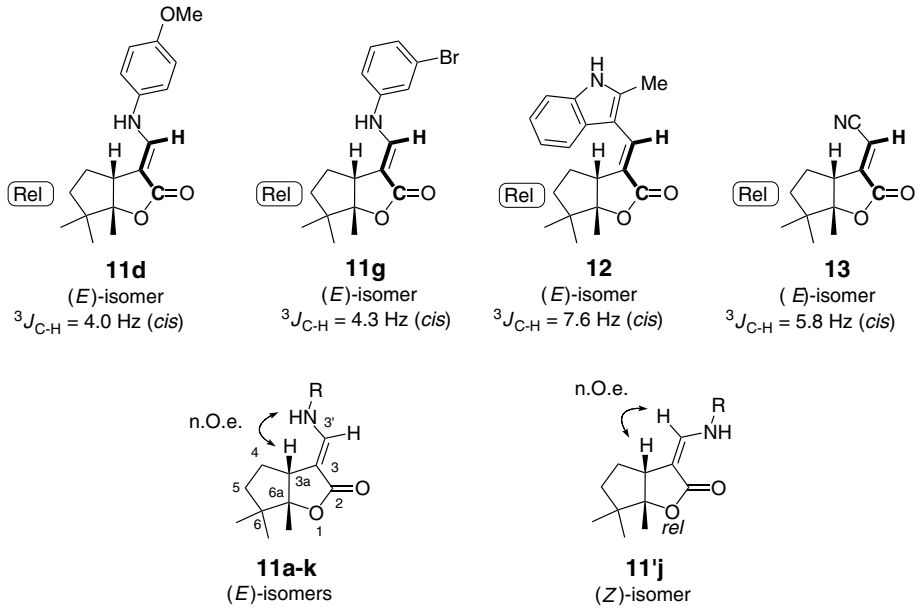


Figure 4. Determination of the configuration around the exocyclic C=C double bond in compounds **11**–**13** by HMBC and NOESY spectroscopy.

Table 2. Correlation between the chemical shifts δ for *H*–C(3″) and N*H* and the *E*/*Z*-configuration around the exocyclic C=C double bond in compounds **11**/**11′**

Compound	Solvent	δ [ppm]			$^3J_{H-H}$ [Hz]		*E* or *Z*
		3′-*H*	N*H*	3a-*H*	CHNH	3a-4	
Major rel-(3aR,6aS,3E)-isomers ***11***							
11a	DMSO-d_6	7.59	8.99	3.27	13.2	9.4	*E*[a]
11b	DMSO-d_6	7.54	8.92	3.24	13.2	9.4	*E*[a]
11c	DMSO-d_6	7.58	9.93	3.26	13.2	9.4	*E*[a]
11d	DMSO-d_6	7.49	8.87	3.22	13.6	9.0	*E*[a,b]
11e	DMSO-d_6	7.58	8.94	3.26	13.2	10.2	*E*[a]
11f	DMSO-d_6	7.56	9.06	3.25	13.2	9.4	*E*[a]
11g	DMSO-d_6	7.59	9.04	3.25	12.8	9.4	*E*[a,b]
11h	DMSO-d_6	7.69	9.60	3.34	11.7	9.4	*E*[a]
11i	DMSO-d_6	7.69	9.34	3.29	12.8	9.4	*E*[a]
11j	DMSO-d_6	7.87	9.62	3.35	12.4	9.8	*E*[a]
11k	DMSO-d_6	—[c]	9.08	3.47	12.4	9.4	*E*[a]
Minor rel-(3aR,6aS,3Z)-isomers ***11′***							
11′e	DMSO-d_6	7.67	9.33	3.14	12.4	9.0	*Z*
11′j	DMSO-d_6	7.92	11.66	3.23	11.8	9.4	*Z*[a]

[a] Determined by NOESY spectroscopy.
[b] Determined by HMBC spectroscopy.
[c] Overlapped by other signals.

yer–Villiger oxidation followed by acid-catalysed rearrangement[31] and condensation with Bredereck's reagent. Finally, the new enaminolactone **6** was assessed in acid-catalysed reactions with electrophiles and nucleophiles. All of these reactions proceeded accordingly to the previously established reactivity of enamino lactone **3**.[24,25,27] Thus, nitrosation of **6** with aqueous $NaNO_2$ gave oxime **9**, while the reactions of **6** with KCN, 2-methyl-1*H*-indole and primary amines **10a**–**k** furnished dimethylamino substitution products **11**–**13**. The reaction of **6** with hydrazine hydrochloride as the ambident nucleophile yielded the 'ring switched' product **14**.

5. Experimental

5.1. General methods

Melting points were determined on a Kofler micro-hot stage. The ^{1}H NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C nucleus, using DMSO-d_6 and $CDCl_3$ with TMS as the internal standard, as solvents. Mass spectra were recorded on an AutoSpecQ spectrometer and IR spectra were recorded on a Perkin–Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a

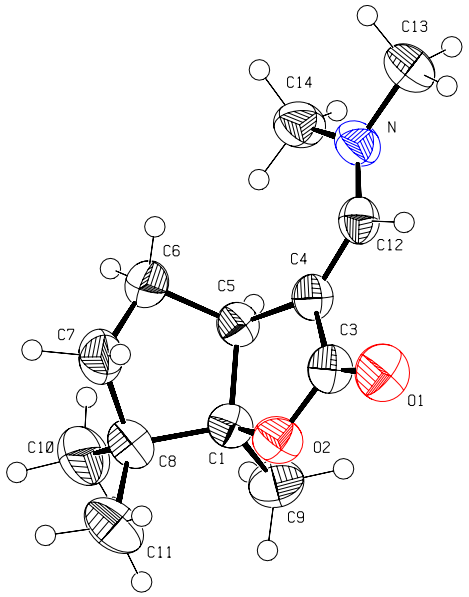


Figure 5. The asymmetric unit of compound **6**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

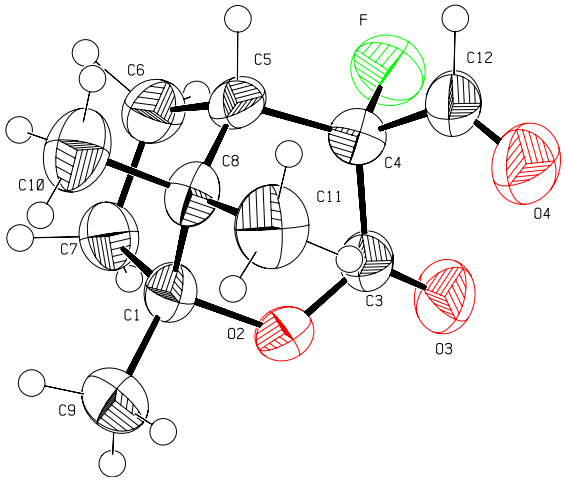


Figure 6. The asymmetric unit of compound **7**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

Perkin–Elmer CHN Analyser 2400. Column chromatography (CC) was performed on silica gel (Fluka, silica gel 60, 0.04–0.06 mm). Medium pressure liquid chromatography (MPLC) was performed with a Büchi isocratic system with detection[†] on silica gel (Merck, silica gel 60, 0.015–0.035 mm); column dimensions (dry filled): 15×460 mm; backpressure: 10–15 bar; detection: UV 254 nm; sample amount: 100–150 mg of isomeric mixture per each run. Ratio of isomers and de were determined by ^{1}H NMR.

A Teflon and nickel vacuum line and system were used as described previously.[61] Moisture-sensitive materials were handled in a dry argon atmosphere in a glove box having a maximum water content of 0.1 ppm of water vapour (M. Braun, Garching, Germany). The reaction vessels made of PFE and equipped with Teflon valves and Teflon coated stirring bars were used for the syntheses. Anhydrous HF (aHF) (Fluka, purum) was treated with K_2NiF_6 (Ozark-Mahoning, 99%) for several days prior to use. Boron trifluoride (Union Carbide, 99.5%) was used as supplied. Xenon difluoride was prepared by photochemical reaction between Xe and F_2 at room temperature.[62] **Caution:** Anhydrous HF must be handled in a well-ventilated hood and protective clothing must be worn at all times!

[†] Donation of Alexander von Humboldt Foundation, Germany.

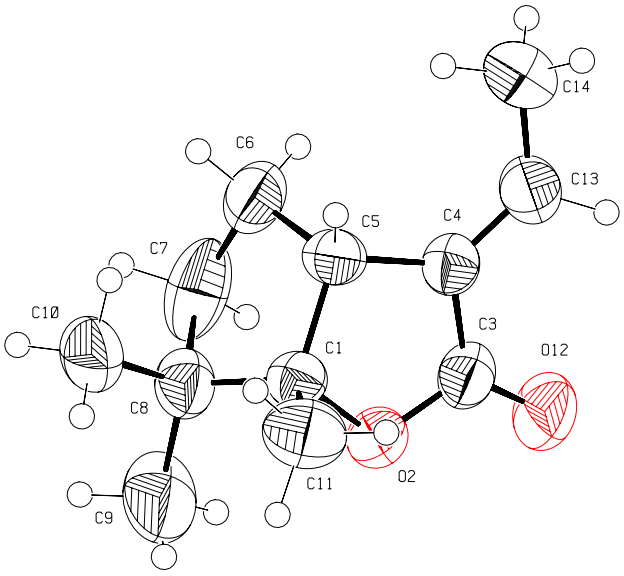


Figure 7. The asymmetric unit of compound **8**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

tert-Butoxy-bis(dimethylamino)methane, sodium nitrite, potassium cyanide, 2-methyl-1*H*-indole, hydrazine hydrochloride, peracetic acid (~39% in AcOH), MeMgBr (3M in Et_2O), tris[3-(heptafluoropropylhydroxymethylene)-D-camphorato] europium(III) and primary amines **10a–k** are commercially available (Fluka AG). (1*R*,4*E*,5*S*)-4-[(Dimethylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one **3**,[24] (1*R*,4*E*,5*S*)-4-ethylidene-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one **4**,[26] a mixture of (1*R*,5*S*)-1,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one **2a** and (1*R*,5*R*)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one **2b**, and a mixture of (1*R*,5*S*)-1,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one **2a** and *rel*-(3a*R*,6a*S*)-6,6,6a-trimethylhexahydrocyclopenta[*b*]furan-2-one **5**[31] were prepared according to the literature procedures.

Source of chirality: (i) (+)-Camphor **1** (Fluka AG), product number 21300, purum, natural, ⩾97.0% (GC, sum of enantiomers), $[\alpha]^{20}_{546} = +54.5 \pm 2.5$ (*c* 10, EtOH), $[\alpha]^{20}_{D} = +42.5 \pm 2.5$ (*c* 10, EtOH), mp 176–180 °C, ee not specified.

5.2. *rel*-(3a*R*,6a*S*,3*E*)-3-[(Dimethylamino)methylidene]-6,6,6a-trimethylhexahydro-2*H*-cyclopenta[*b*]furan-2-one 6

Procedure A: Compound **3** (223 mg, 1 mmol) was weighted into the reaction vessel made of PFE. Anhydrous HF

(3 mL) was condensed at 77 K into the PFE reaction vessel. The clear solution was stirred at room temperature for 16 h and then the aHF was pumped off on the vacuum line. The residue was purified by CC (EtOAc) and MPLC (EtOAc–hexanes, 1:1). Fractions containing the product were combined and evaporated in vacuo to give **6**. Yield: 157 mg (70%) of a white solid.

Procedure B: Compound **3** (223 mg, 1 mmol) was added to a mixture of acetic acid (5 mL) and sulfuric acid (97%, 2 mL) and then stirred at room temperature for 48 h. The reaction mixture was carefully poured into a vigorously stirred saturated aqueous $NaHCO_3$ (200 mL). The resulting mixture was extracted twice with diethyl ether (70 mL), the organic phase dried over anhydrous Na_2SO_4, filtered and the filtrate was evaporated in vacuo. The residue was purified by CC (EtOAc–hexanes, 1:1). Fractions containing the product were combined and evaporated in vacuo to give **6**. Yield: 96 mg (43%) of a white solid.

Procedure C: A mixture of compounds **5** (7.859 g, 46.7 mmol) and **2a** was dissolved in decalin (50 mL). *tert*-Butoxy-bis(dimethylamino)methane (15 mL, 72.6 mmol) was added to the solution, and the mixture heated at reflux for 12 h. Volatile components were evaporated in vacuo and the residue was purified by CC (hexanes–EtOAc, 0:100→100:0). First, elution with hexanes afforded the residues of decalin. Then, elution with EtOAc–hexanes (1:3) afforded **2a** and the unreacted **5**. Finally, elution with EtOAc gave product **6**. Fractions containing the product were combined and evaporated in vacuo to give **6**. Yield: 8.700 g (83%) of a white solid; mp 110–113 °C. ^{1}H NMR ($CDCl_3$): δ 0.91, 1.09, 1.24 (9H, 3s, 1:1:1, 3 × Me); 1.35–1.41, 1.45–1.53, 1.71–1.82 and 1.98–2.12 (4H, 4m, 1:1:1:1, CH_2CH_2); 3.02 (6H, s, NMe_2); 3.28 (1H, br d, $J = 9.4$ Hz, H–C(3a)); 7.11 (1H, d, $J = 1.5$ Hz, H–C(3′)). ^{13}C NMR ($CDCl_3$): δ 19.8, 21.9, 24.0, 33.1, 38.2, 41.7, 44.4, 47.2, 93.4, 95.8, 146.7, 175.1. m/z (EI) = 223 (M^+); m/z (HRMS) Found: 223.157650 (M^+); $C_{13}H_{21}NO_2$ requires: $m/z = 223.157229$. (Found: C, 70.05; H, 9.69; N, 6.59. $C_{13}H_{21}NO_2$ requires: C, 69.92; H, 9.48; N, 6.27.); ν_{max} (KBr) 2963, 2950, 1703 (C=O), 1634, 1617, 1441, 1412, 1385, 1303, 1267, 1236, 1213, 1131, 1103, 1085, 1037 cm^{-1}.

5.3. (1*R*,4*R*,5*S*)-4-Fluoro-1,8,8-trimethyl-3-oxo-2-oxabicyclo[3.2.1]octane-4-carbaldehyde 7

Lactone **3** (223 mg, 1 mmol) was weighed into the reaction vessel made of PFE. Anhydrous acetonitrile (3.110 g) was condensed at 77 K into the PFE reaction vessel. Then, XeF_2 (245.2 mg) was slowly condensed at 77 K. The molar ratio between lactone **3** and XeF_2 was 1:1.24. The thus formed clear solution was stirred at room temperature for 16 h and then the volatile components were pumped off on the vacuum line. The residue was purified by CC (EtOAc–hexanes, 1:3). Fractions containing the product were combined and evaporated in vacuo to give **7**. Yield: 43 mg (20%) of a white solid; mp 72–74 °C; $[\alpha]_D^{23} = -232.6$ (c 0.22, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.90 (3H, s, Me); 1.08 (3H, d, $J = 1.5$ Hz, Me); 1.34 (3H, s, Me); 1.95–2.24 (4H, m, CH_2CH_2); 2.68 (1H, d, $J = 5.7$ Hz, H–C(5)); 9.69 (1H, dd, $J = 0.8$; 1.5 Hz, H–C(4′)). ^{13}C NMR ($CDCl_3$): δ 17.88, 19.19 ($J = 41.1$ Hz), 19.80 (d, $J = 1.44$ Hz), 24.14 (d, $J = 1.44$ Hz), 35.61, 45.73 (d, $J = 5.75$ Hz), 46.33 (d, $J = 16.95$ Hz), 92.11 (d, $J = 183.62$ Hz), 95.60, 165.75 (d, $J = 21.55$ Hz), 190.96 (d, $J = 31.33$ Hz). m/z (EI) = 215 (MH^+). (Found: C, 61.87; H, 7.11. $C_{11}H_{15}FO_3$ requires: C, 61.67; H, 7.06.); ν_{max} (KBr) 1759 (C=O), 1726 (C=O), 1474, 1380, 1345, 1286, 1212, 1153, 1050, 908 cm^{-1}.

5.4. Procedures for the preparation of (3a*R*,6a*S*,3*E*)-3-Ethylidene-6,6,6a-trimethylhexahydro-2*H*-cyclopenta-[*b*]furan-2-one 8

Procedure A: Compound **4** (194 mg, 1 mmol) was weighed into the reaction vessel made of PFE. Anhydrous HF (3 mL) was condensed at 77 K into the PFE reaction vessel. The solution was left stirring at room temperature for 3 h and then the anhydrous HF was pumped off on the vacuum line. The residue was purified by CC (EtOAc–hexanes, 1:8). Fractions containing the product were combined and evaporated in vacuo to give **9**. Yield: 154 mg (79%) of a white solid.

Procedure B: Compound **4** (194 mg, 1 mmol) was added to a mixture of acetic acid (5 mL) and sulfuric acid (97%, 1.5 mL), and the mixture then stirred at room temperature for 120 h. The reaction mixture was poured into water (120 mL), followed by extraction with diethyl ether (twice, 70 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (100 mL) and water (100 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate evaporated in vacuo to give **9**. Yield: 169 mg (87%) of a white solid; mp 63–65 °C (from *n*-hexane); $[\alpha]_D^{23} = +185.7$ (c 0.28, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.94, 1.10, 1.27 (9H, 3s, 1:1:1, 3 × Me); 1.41–1.48 and 1.64–1.75 (3H, 2m, 2:1, 3H of CH_2); 1.86 (3H, dd, $J = 1.1$, 7.2 Hz, H_3C–C(3′)); 2.09–2.24 (1H, m, 1H of CH_2); 3.11 (1H, br d, $J = 9.8$ Hz, H–C(3a)); 6.74 (1H, dd, $J = 2.3$; 7.2 Hz, H–C(3′)). ^{13}C NMR ($CDCl_3$): δ 15.7, 20.5, 22.1, 24.3, 30.6, 38.9, 45.1, 47.2, 96.0, 135.4, 135.8, 171.3. m/z (EI) = 194 (M^+); m/z (HRMS) Found: 194.131060 (M^+); $C_{12}H_{18}O_2$ requires: $m/z = 194.130680$. (Found: C, 73.87; H, 9.50. $C_{12}H_{18}O_2$ requires: C, 74.19; H, 9.34.); ν_{max} (KBr) 2963, 1745 (C=O), 1675, 1466, 1377, 1279, 1244, 1219, 1121, 1041, 1006, 977, 924 cm^{-1}.

5.5. *rel*-(3a*R*,6a*S*,3*E*)-3-Ethylidene-6,6,6a-trimethylhexahydro-2*H*-cyclopenta[*b*]furan-2-one *rac*-8

A solution of **6** (223 mg, 1 mmol) in anhydrous THF (3 mL) was cooled to −78 °C under argon and a solution of MeMgBr in Et_2O (3 M, 7 mL, 21 mmol) was added slowly in a period of 5 min. The mixture was stirred at −78 °C for 1 h, warmed up to rt and stirred at rt for an additional 48 h. Saturated aqueous NH_4Cl (10 mL) was then added, the mixture stirred at rt for 1 h, poured into brine (20 mL) and the product extracted with CH_2Cl_2 (3 × 70 mL). The organic phases were combined, dried over anhydrous Na_2SO_4, filtered and the filtrate was evaporated in vacuo. The residue was purified by CC (EtOAc–hexanes, 1:2). Fractions containing the product were combined and evaporated in vacuo to give the crude product *rac*-**8**, which

was additionally purified by MPLC (EtOAc–hexanes, 1:11). Fractions containing the product were combined and evaporated in vacuo to give *rac*-**8**. Yield: 45 mg (23%) of a white solid; mp 63–65 °C (from *n*-hexane). ^{1}H NMR ($CDCl_3$): δ 0.94, 1.10, 1.27 (9H, 3s, 1:1:1, 3 × Me); 1.41–1.48, 1.64–1.75 (3H, 2m, 2:1, 3H of CH_2); 1.86 (3H, dd, $J = 1.1$; 7.2 Hz, H_3C–C(3′)); 2.09–2.24 (1H, m, 1H of CH_2); 3.11 (1H, br d, $J = 9.8$ Hz, H–C(3a)); 6.74 (1H, dd, $J = 2.3$; 7.2 Hz, H–C(3′)); ν_{max} (KBr) 2963, 1745 (C=O), 1675, 1466, 1377, 1279, 1244, 1219, 1121, 1041, 1006, 977, 924 cm^{-1}.

5.6. *rel*-(3a*R*,6a*S*,3*E*)-3-(Hydroxyimino)-6,6,6a-trimethylhexahydro-2*H*-cyclopenta[*b*]furan-2-one 9

Hydrochloric acid (1 M, 10 mL, 10 mmol) was added slowly to a stirred suspension of compound **6** (2.010 g, 9 mmol) in aqueous $NaNO_2$ (0.3 M, 60 mL, 18 mmol), stirred at 0 °C for 0.5 h and then at rt for 1 h. Afterwards, acetic acid (10 mL) was added and the mixture was stirred at rt for another 1.5 h. The precipitate was collected by filtration and washed with water (100 mL) to give the first portion of product **8** (1.248 g). The filtrate was neutralised with excess saturated aqueous $NaHCO_3$ (200 mL) and the resulting mixture extracted twice with CH_2Cl_2 (100 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the filtrate was evaporated in vacuo. The residue was crystallised from the $CHCl_3$–*n*-heptane to give the second portion of product **8** (401 mg). Yield: 1.649 g (93%) of a white solid; mp 177–181 °C. ^{1}H NMR ($CDCl_3$): δ 0.95, 1.12, 1.34 (9H, 3s, 1:1:1, 3 × Me); 1.48–1.57, 1.62–1.77, 2.13–2.28 (4H, 3m, 1:2:1, CH_2CH_2); 3.43 (1H, dd, $J = 1.5$; 10.2 Hz, H–C(3a)); 9.15 (1H, br s, OH). ^{13}C NMR ($CDCl_3$): δ 20.7, 21.7, 24.1, 27.5, 38.9, 45.3, 46.6, 97.5, 153.8, 166.3. *m*/*z* (EI) = 198 (MH^+); *m*/*z* (HRMS) Found: 198.113650 (MH^+); $C_{10}H_{16}NO_3$ requires: *m*/*z* = 198.113019. (Found: C, 60.24; H, 7.62; N, 8.95. $C_{10}H_{15}NO_3$ requires: C, 60.90; H, 7.67; N, 7.10.); ν_{max} (KBr) 3351, 2967, 2935, 2876, 1754 (C=O), 1659, 1468, 1433, 1394, 1323, 1298, 1276, 1123, 1054, 1000, 926, 906, 864 cm^{-1}.

5.7. General procedures for the preparation of N-substituted *rel*-(3a*R*,6a*S*,3*E*)-6,6,6a-trimethyl-3-(aminomethylidene)-hexahydrocyclopenta[*b*]furan-2-ones 11a–k and their *rel*-(3a*R*,6a*S*,3*Z*)-isomers 11′e,j

Procedure A: Amine hydrochloride **10a** or **10b** (1 mmol) was added to a solution of compound **6** (223 mg, 1 mmol) in anhydrous ethanol (3 mL) and the mixture stirred at rt for 24 h. The precipitate was collected by filtration and washed with cold ethanol (0 °C, 1 mL) to give **11a** and **11b**, respectively.

Procedure B: Compound **6** (223 mg, 1 mmol) was added to a solution of amine **10c**–**k** (1 mmol) in a mixture of anhydrous ethanol (3 mL) and sulfuric acid (97%, 0.027 mL, 0.5 mmol), and the mixture was stirred at reflux for 1.5 h and at rt for 24 h. In the case of the reactions with amines **10c**,**d**,**f**–**i**,**k**, the precipitate was collected by filtration and washed with cold ethanol (0 °C, 1 mL) to give **11c**,**d**,**f**–**i**,**k**. In the case of the reaction with amine **10j**, the reaction mixture was filtered to remove the precipitated black impurities and the filtrate was cooled to 0 °C. The precipitate was collected by filtration to give **11j**. In the case of the reaction with amine **10e**, water (4 mL) was slowly added to the reaction mixture. The so formed precipitate was collected by filtration to give **11e**.

5.7.1. *rel*-(3a*R*,6a*S*,3*E*)-6,6,6a-Trimethyl-3-[(phenylamino)-methylidene]hexahydrocyclopenta[*b*]furan-2-one 11a. Prepared from **6** and aniline hydrochloride **10a** (130 mg, 1 mmol); Procedure A; 155 mg (57%) of a white solid; mp 220–223 °C. ^{1}H NMR (DMSO-d_6): δ 0.92, 1.02, 1.20 (9H, 3s, 1:1:1, 3 × Me); 1.33–1.59 and 2.03–2.17 (4H, 2m, 3:1, CH_2CH_2); 3.27 (1H, br d, $J = 9.4$ Hz, H–C(3a)); 6.92–6.97 (1H, m, 1H of Ph); 7.16 (2H, d, $J = 7.9$ Hz, 2H of Ph); 7.26–7.31 (2H, m, 2H of Ph); 7.59 (1H, dd, $J = 1.5$; 13.2 Hz, H–C(3′)); 8.99 (1H, br d, $J = 13.2$ Hz, NH). ^{13}C NMR (DMSO-d_6): δ 20.9, 22.6, 24.6, 30.8, 39.2, 45.0, 46.8, 94.4, 104.3, 116.1, 122.5, 130.3, 135.7, 142.5, 172.8. *m*/*z* (EI) = 271 (M^+); *m*/*z* (HRMS) Found: 271.158020 (M^+); $C_{17}H_{21}NO_2$ requires: *m*/*z* = 271.157229. (Found: C, 75.44; H, 8.02; N, 5.24. $C_{17}H_{21}NO_2$ requires: C, 75.25; H, 7.80; N, 5.16.); ν_{max} (KBr) 3426, 3279, 2958, 1717 (C=O), 1631, 1601, 1590, 1499, 1275, 1242, 1118, 1084, 1040 cm^{-1}.

5.7.2. *rel*-(3a*R*,6a*S*,3*E*)-3-[(4-Methylphenylamino)methylidene]-6,6,6a-trimethylhexahydrocyclopenta[*b*]furan-2-one 11b. Prepared from **6** and 4-methylaniline hydrochloride **10b** (144 mg, 1 mmol); Procedure A; 89 mg (31%) of a white solid; mp 226–229 °C. ^{1}H NMR (DMSO-d_6): δ 0.91, 1.01, 1.19 (9H, 3s, 1:1:1, 3 × Me); 1.32–1.58 and 2.02–2.16 (4H, 2m, 3:1, CH_2CH_2); 2.23 (3H, s, *Me*–Ar); 3.24 (1H, br d, $J = 9.4$ Hz, H–C(3a)); 7.03–7.11 (4H, m, C_6H_4); 7.54 (1H, dd, $J = 1.5$; 13.2 Hz, H–C(3′)); 8.92 (1H, br d, $J = 13.2$ Hz, NH). ^{13}C NMR (DMSO-d_6): δ 20.9, 21.1, 22.6, 24.6, 30.8, 39.2, 45.0, 46.8, 94.3, 103.5, 116.2, 130.7, 131.4, 136.0, 140.1, 172.8. *m*/*z* (EI) = 285 (M^+); *m*/*z* (HRMS) Found: 285.172120 (M^+); $C_{18}H_{23}NO_2$ requires: *m*/*z* = 285.172879. (Found: C, 75.78; H, 8.34; N, 5.11. $C_{18}H_{23}NO_2$ requires: C, 75.76; H, 8.12; N, 4.91.); ν_{max} (KBr) 3424, 3277, 2953, 1715 (C=O), 1630, 1611, 1592, 1526, 1273, 1240, 1117, 1040 cm^{-1}.

5.7.3. *rel*-(3a*R*,6a*S*,3*E*)-3-[(3-Methylphenylamino)methylidene]-6,6,6a-trimethylhexahydrocyclopenta[*b*]furan-2-one 11c. Prepared from **6** and 3-methylaniline **10c** (107 mg, 1 mmol); Procedure B; 92 mg (32%) of a white solid; mp 184–187 °C. ^{1}H NMR (DMSO-d_6): δ 0.91, 1.02, 1.19 (9H, 3s, 1:1:1, 3 × Me); 1.32–1.58 and 2.03–2.17 (4H, 2m, 3:1, CH_2CH_2); 2.28 (3H, s, *Me*–Ar); 3.26 (1H, br d, $J = 9.4$ Hz, H–C(3a)); 6.77 (1H, d, $J = 7.5$ Hz, 1H of C_6H_4); 6.93–6.99 (2H, m, 2H of C_6H_4); 7.16 (1H, degenerate t, $J = 7.5$; 7.9 Hz, 1H of C_6H_4); 7.58 (1H, dd, $J = 1.5$; 13.2 Hz, H–C(3′)); 8.93 (1H, br d, $J = 13.2$ Hz, NH). ^{13}C NMR (DMSO-d_6): δ 20.9, 22.0, 22.6, 24.6, 30.8, 39.2, 45.0, 46.8, 94.4, 104.1, 113.5, 116.6, 123.3, 130.1, 135.7, 139.7, 142.4, 172.8. *m*/*z* (EI) = 285 (M^+); *m*/*z* (HRMS) Found: 285.173550 (M^+); $C_{18}H_{23}NO_2$ requires: *m*/*z* = 285.172879. (Found: C, 74.81; H, 8.12; N, 5.83. $C_{18}H_{23}NO_2$ requires: C, 75.76; H, 8.12; N, 4.91.); ν_{max}

(KBr) 3428, 3275, 2964, 1715 (C=O), 1630, 1597, 1385, 1254, 1234, 1119, 1042 cm^{-1}.

5.7.4. *rel*-(3a*R*,6a*S*,3*E*)-3-[(4-Methoxyphenylamino)methylidene]-6,6,6a-trimethylhexahydrocyclopenta[*b*]furan-2-one 11d. Prepared from **6** and 4-methoxyaniline **10d** (123 mg, 1 mmol); Procedure B; 187 mg (62%) of a white solid; mp 225–230 °C. ^{1}H NMR (DMSO-d_6): δ 0.91, 1.01, 1.19 (9H, 3s, 1:1:1, 3Me); 1.32–1.58 and 2.01–2.15 (4H, 2m, 3:1, CH_2CH_2); 3.22 (1H, br d, $J = 9.0$ Hz, H–C(3a)); 3.71 (3H, s, OMe); 6.85–6.91 (2H, m, 2H of C_6H_4); 7.07–7.12 (2H, m, 2H of C_6H_4); 7.49 (1H, dd, $J = 1.5$; 13.6 Hz, H–C(3′)); 8.87 (1H, br d, $J = 13.6$ Hz, NH). ^{13}C NMR (DMSO-d_6): δ 20.9, 22.7, 24.6, 30.8, 39.2, 45.0, 46.9, 56.1, 94.2, 102.8, 115.6, 117.6, 136.0, 136.7, 155.4, 172.8. *m*/*z* (EI) = 301 (M^+); *m*/*z* (HRMS) Found: 301.168350 (M^+); $C_{18}H_{23}NO_3$ requires: *m*/*z* = 301.167794. (Found: C, 71.80; H, 7.84; N, 4.82. $C_{18}H_{23}NO_3$ requires: C, 71.73; H, 7.69; N, 4.65.); ν_{max} (KBr) 3426, 3283, 2965, 1716 (C=O), 1627, 1594, 1522, 1506, 1239, 1117, 1041 cm^{-1}.

5.7.5. *rel*-(3a*R*,6a*S*,3*E*)-3-[(3-Methoxyphenylamino)methylidene]-6,6,6a-trimethylhexahydrocyclopenta[*b*]furan-2-one 11e and its *rel*-(3a*R*,6a*S*,3*Z*)-isomer 11′e. Prepared from **6** and 3-methoxyaniline **10e** (123 mg, 1 mmol); Procedure B; 202 mg (67%) of a greyish-white solid; **11e**:**11′e** = 93:7; mp 164–167 °C. *m*/*z* (EI) = 301 (M^+); *m*/*z* (HRMS) Found: 301.168560 (M^+); $C_{18}H_{23}NO_3$ requires: *m*/*z* = 301.167794. (Found: C, 71.88; H, 7.83; N, 4.55. $C_{18}H_{23}NO_3$ requires: C, 71.73; H, 7.69; N, 4.65.); ν_{max} (KBr) 3424, 3281, 2964, 1715 (C=O), 1629, 1594, 1462, 1282, 1260, 1234, 1198, 1152, 1119, 1042 cm^{-1}.

5.7.5.1. NMR data for major *rel*-(3a*R*,6a*S*,3*E*)-isomer 11e. ^{1}H NMR (DMSO-d_6): δ 0.91, 1.02, 1.20 (9H, 3s, 1:1:1, 3 × Me); 1.32–1.59 and 2.03–2.17 (4H, 2m, 3:1, CH_2CH_2); 3.26 (1H, br d, $J = 10.2$ Hz, H–C(3a)); 3.75 (3H, s, OMe); 6.50–6.54 (1H, m, 1H of C_6H_4); 6.70–6.76 (2H, m, 2H of C_6H_4); 7.18 (1H, deg t, $J = 7.9$; 8.3 Hz, 1H of C_6H_4); 7.58 (1H, dd, $J = 1.5$; 13.2 Hz, H–C(3′)); 8.94 (1H, br d, $J = 13.2$ Hz, NH). ^{13}C NMR (DMSO-d_6): δ 20.8, 22.6, 24.6, 30.8, 39.1, 45.0, 46.8, 55.9, 94.4, 101.9, 104.5, 108.3, 108.5, 131.2, 135.7, 143.8, 161.2, 172.7.

5.7.5.2. NMR data for minor *rel*-(3a*R*,6a*S*,3*Z*)-isomer 11′e. ^{1}H NMR (DMSO-d_6): δ 0.90, 1.23 (6H, 2s, 1:1, 2 × Me); 3.14 (1H, br d, $J = 9.0$ Hz, H–C(3a)); 6.80–6.81 (1H, m, 1H of C_6H_4); 7.17 (1H, deg t, $J = 7.9$; 8.3 Hz, 1H of C_6H_4); 7.67 (1H, d, $J = 11.7$ Hz, H–C(3′)); 9.33 (1H, br d, $J = 12.4$ Hz, NH).

5.7.6. *rel*-(3a*R*,6a*S*,3*E*)-3-[(4-Bromophenylamino)methylidene]-6,6,6a-trimethylhexahydrocyclopenta[*b*]furan-2-one 11f. Prepared from **6** and 4-bromoaniline **10f** (172 mg, 1 mmol); Procedure B; 221 mg (63%) of a white solid; mp 217–219 °C. ^{1}H NMR (DMSO-d_6): δ 0.91, 1.02, 1.20 (9H, 3s, 1:1:1, 3 × Me); 1.33–1.58 and 2.03–2.17 (4H, 2m, 3:1, CH_2CH_2); 3.25 (1H, br d, $J = 9.4$ Hz, H–C(3a)); 7.11–7.16 (2H, m, 2H of C_6H_4); 7.41–7.46 (2H, m, 2H of C_6H_4); 7.56 (1H, dd, $J = 1.5$; 13.2 Hz, H–C(3′)); 9.06 (1H, br d, $J = 13.2$ Hz, NH). ^{13}C NMR (DMSO-d_6): δ 20.8, 22.6, 24.6, 30.8, 39.1, 45.0, 46.8, 94.6, 105.3, 113.9, 118.1, 132.9, 135.2, 141.9, 172.6. *m*/*z* (EI) = 349 (M^+); *m*/*z* (HRMS) Found: 349.067740 (M^+); $C_{17}H_{20}BrNO_2$ requires: *m*/*z* = 349.067740. (Found: C, 58.28; H, 5.94; N, 3.95. $C_{17}H_{20}BrNO_2$ requires: C, 58.30; H, 5.76; N, 4.00.); ν_{max} (KBr) 3429, 3269, 2960, 1719 (C=O), 1639, 1595, 1584, 1516, 1487, 1241, 1119, 1041 cm^{-1}.

5.7.7. *rel*-(3a*R*,6a*S*,3*E*)-3-[(3-Bromophenylamino)methylidene]-6,6,6a-trimethylhexahydrocyclopenta[*b*]furan-2-one 11g. Prepared from **6** and 3-bromoaniline **10g** (172 mg, 1 mmol); Procedure B; 179 mg (51%) of a white solid; mp 216–220 °C. ^{1}H NMR (DMSO-d_6): δ 0.91, 1.02, 1.20 (9H, 3s, 1:1:1, 3 × Me); 1.33–1.58 and 2.03–2.17 (4H, 2m, 3:1, CH_2CH_2); 3.25 (1H, br d, $J = 9.4$ Hz, H–C(3a)); 7.08–7.31 (3H, m, 3H of C_6H_4); 7.37–7.39 (1H, m, 1H of C_6H_4); 7.59 (1H, dd, $J = 1.5$; 13.2 Hz, H–C(3′)); 9.04 (1H, br d, $J = 12.8$ Hz, NH). ^{13}C NMR (DMSO-d_6): δ 20.8, 22.6, 24.6, 30.8, 39.1, 45.0, 46.8, 94.6, 105.9, 114.8, 118.9, 123.2, 124.9, 132.2, 135.1, 144.2, 172.5. *m*/*z* (EI) = 349 (M^+); *m*/*z* (HRMS) Found: 349.068560 (M^+); $C_{17}H_{20}BrNO_2$ requires: *m*/*z* = 349.067740. (Found: C, 59.62; H, 6.07; N, 4.12. $C_{17}H_{20}BrNO_2$ requires: C, 58.30; H, 5.76; N, 4.00.); ν_{max} (KBr) 3437, 3269, 2966, 1719 (C=O), 1642, 1597, 1472, 1273, 1250, 1223, 1120, 1042 cm^{-1}.

5.7.8. *rel*-(3a*R*,6a*S*,3*E*)-3-[(4-Nitrophenylamino)methylidene]-6,6,6a-trimethylhexahydrocyclopenta[*b*]furan-2-one 11h. Prepared from **6** and 4-bromoaniline **10h** (138 mg, 1 mmol); Procedure B; 136 mg (43%) of a yellow solid; mp 270–275 °C. ^{1}H NMR (DMSO-d_6): δ 0.92, 1.03, 1.22 (9H, 3s, 1:1:1, 3 × Me); 1.35–1.60 and 2.08–2.22 (4H, 2m, 3:1, CH_2CH_2); 3.34 (1H, br d, $J = 9.4$ Hz, H–C(3a)); 7.35–7.40 (2H, m, 2H of C_6H_4); 7.69 (1H, br d, $J = 10.5$ Hz, H–C(3′)); 8.13–8.18 (2H, m, 3H of C_6H_4); 9.60 (1H, br d, $J = 11.7$ Hz, NH). ^{13}C NMR (DMSO-d_6): δ 20.7, 22.5, 24.5, 30.9, 39.1, 45.0, 46.8, 95.1, 109.5, 115.7, 126.6, 133.7, 141.5, 148.6, 172.2. *m*/*z* (EI) = 316 (M^+); *m*/*z* (HRMS) Found: 316.143030 (M^+); $C_{17}H_{20}N_2O_4$ requires: *m*/*z* = 316.142307. (Found: C, 64.57; H, 6.48; N, 8.88. $C_{17}H_{20}N_2O_4$ requires: C, 64.54; H, 6.37; N, 8.86.); ν_{max} (KBr) 2961, 1718 (C=O), 1661, 1640, 1589, 1508, 1494, 1331, 1275, 1242, 1225, 1192, 1111, 1042 cm^{-1}.

5.7.9. *rel*-(3a*R*,6a*S*,3*E*)-3-[(3-Nitrophenylamino)methylidene]-6,6,6a-trimethylhexahydrocyclopenta[*b*]furan-2-one 11i. Prepared from **6** and 3-bromoaniline **10i** (138 mg, 1 mmol); Procedure B; 73 mg (23%) of a red solid; mp 226–232 °C. ^{1}H NMR (DMSO-d_6): δ 0.93, 1.03, 1.22 (9H, 3s, 1:1:1, 3 × Me); 1.36–1.60 and 2.06–2.20 (4H, 2m, 3:1, CH_2CH_2); 3.29 (1H, br d, $J = 9.4$ Hz, H–C(3a)); 7.55 (1H, deg t, $J = 7.9$; 8.3 Hz, 1H of C_6H_4); 7.65–7.77 (3H, m, 2H of C_6H_4, H–C(3′)); 7.99 (1H, t, $J = 2.3$ Hz, 1H of C_6H_4); 9.34 (1H, br d, $J = 12.8$ Hz, NH). ^{13}C NMR (DMSO-d_6): δ 20.8, 22.6, 24.5, 30.8, 39.1, 45.0, 46.8, 94.8, 107.0, 110.9, 116.4, 121.5, 131.7, 134.7, 143.8, 149.5, 172.4. *m*/*z* (EI) = 316 (M^+); *m*/*z* (HRMS) Found: 316.143050 (M^+); $C_{17}H_{20}N_2O_4$ requires: *m*/*z* = 316.142307. (Found: C, 64.68; H, 6.57; N, 8.84. $C_{17}H_{20}N_2O_4$ requires: C, 64.54; H, 6.37; N, 8.86.); ν_{max}

(KBr) 2959, 1719 (C=O), 1663, 1637, 1618, 1589, 1540, 1524, 1348, 1241, 1225, 1118, 1043 cm^{-1}.

5.7.10. *rel*-(3a*R*,6a*S*,3*E*)-3-[(2-Nitrophenylamino)methylidene]-6,6,6a-trimethylhexahydrocyclopenta[*b*]furan-2-one 11j and its *rel*-(3a*R*,6a*S*,3*Z*)-isomer 11′j. Prepared from **6** and 2-nitroaniline **10j** (138 mg, 1 mmol); Procedure B; 64 mg (20%) of a red solid; **11j**:**11′j** = 63:37; mp 165–185 °C. ^{13}C NMR (DMSO-d_6): δ 20.8, 21.2, 22.7, 22.8, 24.4, 24.5, 29.4, 33.9, 39.1, 39.3, 45.06, 45.09, 46.7, 48.3, 95.5, 96.8, 109.0, 111.4, 116.6, 117.7, 121.6, 122.2, 127.08, 127.15, 133.2, 134.8, 135.8, 136.2, 137.2, 137.4, 138.1, 138.2, 171.6, 172.2. *m*/*z* (EI) = 316 (M^+); *m*/*z* (HRMS) Found: 316.142250 (M^+); $C_{17}H_{20}N_2O_4$ requires: *m*/*z* = 316.142307. (Found: C, 64.71; H, 6.56; N, 8.98. $C_{17}H_{20}N_2O_4$ requires: C, 64.54; H, 6.37; N, 8.86.); ν_{max} (KBr) 2967, 1737 (C=O), 1708 (C=O), 1659, 1608, 1580, 1503, 1385, 1342, 1260, 1213, 1189, 1113, 1041 cm^{-1}.

5.7.10.1. NMR data for the major *rel*-(3a*R*,6a*S*,3*E*)-isomer 11j. ^1H NMR (DMSO-d_6): δ 0.95, 1.03, 1.25 (9H, 3s, 1:1:1, 3 × Me); 1.40–1.65 and 2.09–2.28 (4H, 2m, 3:1, CH_2CH_2); 3.35 (1H, br d, J = 9.8 Hz, H–C(3a)); 7.35–7.40 (2H, m, 2H of C_6H_4); 7.87 (1H, dd, J = 1.8; 12.4 Hz, H–C(3′)); 8.13–8.18 (2H, m, 1H of C_6H_4); 9.62 (1H, br d, J = 12.4 Hz, NH).

5.7.10.2. NMR data for the minor *rel*-(3a*R*,6a*S*,3*Z*)-isomer 11′j. ^1H NMR (DMSO-d_6): δ 0.92, 1.03, 1.26 (9H, 3s, 1:1:1, 3 × Me); 3.23 (1H, br d, J = 9.4 Hz, H–C(3a)); 7.35–7.40 (2H, m, 2H of C_6H_4); 7.92 (1H, dd, J = 1.0; 11.9 Hz, H–C(3′)); 8.13–8.18 (2H, m, 2H of C_6H_4); 11.66 (1H, br d, J = 11.7 Hz, NH).

5.7.11. *rel*-(3a*R*,6a*S*,3*E*)-3-[(Naphth-1-ylamino)methylidene]-6,6,6a-trimethylhexahydrocyclopenta[*b*]furan-2-one 11k. Prepared from **6** and naphthalen-1-amine **10k** (143 mg, 1 mmol); Procedure B; 193 mg (60%) of a white solid; mp 210–214 °C. ^1H NMR (DMSO-d_6): δ 0.93, 1.04, 1.23 (9H, 3s, 1:1:1, 3 × Me); 1.42–1.63 and 2.08–2.21 (4H, 2m, 3:1, CH_2CH_2); 3.47 (1H, br d, J = 9.4 Hz, H–C(3a)); 7.26 (1H, br d, J = 7.2 Hz, 1H of $C_{10}H_7$); 7.45–7.68 (5H, m, 4H of $C_{10}H_7$, H–C(3′)); 7.91–7.95 (1H, m, 1H of $C_{10}H_7$); 8.18–8.21 (1H, m, 1H of $C_{10}H_7$); 9.08 (1H, br d, J = 12.4 Hz, NH). ^{13}C NMR (DMSO-d_6): δ 21.0, 22.7, 24.6, 30.9, 39.2, 45.0, 46.9, 94.4, 105.1, 115.7, 123.5, 124.4, 126.5, 126.7, 127.1, 127.3, 129.0, 134.8, 138.9, 139.2, 173.0. *m*/*z* (EI) = 321 (M^+); *m*/*z* (HRMS) Found: 321.173550 (M^+); $C_{21}H_{23}NO_2$ requires: *m*/*z* = 321.172879. (Found: C, 78.37; H, 7.39; N, 4.32. $C_{21}H_{23}NO_2$ requires: C, 78.47; H, 7.21; N, 4.36.); ν_{max} (KBr) 3433, 3291, 2963, 1709 (C=O), 1633, 1621, 1578, 1398, 1385, 1239, 1121 cm^{-1}.

5.8. *rel*-(3a*R*,6a*S*,3*E*)-3-[(2-Methyl-1*H*-indol-3-yl)methylidene]-6,6,6a-trimethylhexahydrocyclopenta[*b*]furan-2-one 12

A mixture of **6** (223 mg, 1 mmol), 2-methyl-1*H*-indole (131 mg, 1 mmol) and acetic acid (3 mL) was stirred at reflux for 7 h. Volatile components were evaporated in vacuo and the residue was purified by CC (EtOAc–petroleum ether, 1:2). Fractions containing the product were combined and evaporated in vacuo to give **12**. Yield: 267 mg (86%) of a yellow solid; mp 79–84 °C. ^1H NMR (DMSO-d_6): δ 0.96, 1.04, 1.28 (9H, 3s, 1:1:1, 3 × Me); 1.36–1.44, 1.49–1.59 and 2.10–2.24 (4H, 3m, 2:1:1, CH_2CH_2); 2.51 (3H, s, Me); 3.66 (1H, br d, J = 9.8 Hz, H–C(3a)); 7.08–7.16 and 7.33–7.38 (3H, 2m, 2:1, 3H of Ar); 7.53 (1H, d, J = 1.9 Hz, H–C(3′)); 7.70–7.73 (1H, m, 1H of Ar); 11.75 (1H, br s, NH). ^{13}C NMR (DMSO-d_6): δ 13.2, 20.9, 22.8, 24.4, 32.2, 39.0, 45.1, 49.6, 94.5, 108.3, 112.2, 120.4, 121.3, 122.4, 124.1, 126.5, 130.5, 136.8, 142.6, 173.0. *m*/*z* (EI) = 309 (M^+); *m*/*z* (HRMS) Found: 309.173550 (M^+); $C_{20}H_{23}NO_2$ requires: *m*/*z* = 309.172879. (Found: C, 77.21; H, 8.02; N, 5.50. $C_{20}H_{23}NO_2$ requires: C, 77.64; H, 7.49; N, 4.53.); ν_{max} (KBr) 3246, 3223, 2959, 2930, 2870, 1714 (C=O), 1621, 1459, 1386, 1278, 1240, 1221, 1120, 1098, 1048 cm^{-1}.

5.9. *rel*-2-[(3*E*,3a*R*,6a*S*)-6,6,6a-Trimethyl-2-oxo-tetrahydro-2*H*-cyclopenta[*b*]furan-3(3a*H*)-ylidene]acetonitrile 13

KCN (130 mg, 2 mmol) was added to a solution of **6** (223 mg, 1 mmol) in acetic acid (3 mL) and the mixture stirred at room temperature for 120 h. Volatile components were evaporated in vacuo and the residue was suspended in CH_2Cl_2 (50 mL). The thus formed suspension was filtered, the undissolved material washed with CH_2Cl_2 (50 mL) and the filtrate was evaporated in vacuo. The residue was purified by CC (EtOAc–petroleum ether, 1:5). Fractions containing the product were combined and evaporated in vacuo to give **13**. Yield: 130 mg (63%) of a white solid; mp 97–99 °C. ^1H NMR ($CDCl_3$): δ 0.97, 1.12, 1.34 (9H, 3s, 1:1:1, 3 × Me); 1.52–1.77 and 2.37–2.53, (4H, 2m, 3:1, CH_2CH_2); 3.41–3.46 (1H, m, H–C(3a)); 6.25 (1H, d, J = 2.3 Hz, H–C(3′)). ^{13}C NMR ($CDCl_3$): δ 20.4, 21.9, 24.1, 31.1, 38.8, 45.2, 50.1, 98.1, 104.2, 115.4, 156.4, 167.7. *m*/*z* (EI) = 205 (M^+); *m*/*z* (HRMS) Found: 205.110850 (M^+); $C_{12}H_{15}NO_2$ requires: *m*/*z* = 205.110279. (Found: C, 70.12; H, 7.62; N, 7.73. $C_{12}H_{15}NO_2$ requires: C, 70.22; H, 7.37; N, 6.82.); ν_{max} (KBr) 3057, 2959, 2219 (C≡N), 1763 (C=O), 1466, 1391, 1294, 1257, 1221, 1126, 1056 cm^{-1}.

5.10. *rel*-4-[(1*S*,2*R*)-2-Hydroxy-2,3,3-trimethylcyclopentyl]-1*H*-pyrazol-3-ol 14

A mixture of **6** (223 mg, 1 mmol) and hydrazine hydrochloride (69 mg, 1 mmol) in anhydrous ethanol (3 mL) was stirred at reflux for 7 h. Volatile components were evaporated in vacuo and the residue was purified by CC ($CHCl_3$–MeOH, 15:1). Fractions containing the product were combined and evaporated in vacuo to give **14**. Yield: 200 mg (95%) of a white solid; mp 209–219 °C. ^1H NMR (DMSO-d_6): δ 0.88, 0.90, 0.95 (9H, 3s, 1:1:1, 3 × Me); 1.32–1.41 and 1.58–1.83 (4H, 2m, 1:3, CH_2CH_2); 2.95–3.02 (1H, m, H–C(4′)); 4.29 (1H, br s, HO–C(2')); 7.23 (1H, s, H–C(5)); 9.77 (1H, br s, NH); 10.90 (1H, br s, HO–C(3)). ^{13}C NMR (DMSO-d_6): δ 20.3, 23.8, 28.2, 28.8, 38.0, 42.8, 45.9, 83.4, 103.9, 130.1, 160.2. *m*/*z* (EI) = 210 (M^+); *m*/*z* (HRMS) Found: 210.136900 (M^+); $C_{11}H_{18}N_2O_2$ requires: *m*/*z* = 210.136828. (Found: C, 62.58; H, 8.86; N, 13.40. $C_{11}H_{18}N_2O_2$ requires: C, 62.83; H, 8.63; N, 13.32.); ν_{max} (KBr) 3456, 3180, 3142, 2958,

2874, 2803, 2686, 1605, 1526, 1470, 1389, 1369, 1177, 1100, 1071 cm^{-1}.

5.11. X-ray structure analysis for compounds 6–8

Single crystal X-ray diffraction data of compounds **6**, **7** and **8** were collected at room temperature on a Nonius Kappa CCD diffractometer using the Nonius Collect Software.[63] DENZO and SCALEPACK[64] were used for indexing and scaling of the data and the structures were solved by means of SIR97.[65] Refinement and plotting were done using Xtal3.4[66] program package. Crystal structures were refined on *F* values using the full-matrix least-squares procedure. The non-hydrogen atoms were refined anisotropically in all cases, while the positions of the hydrogen atoms were geometrically calculated and their positional and isotropic atomic displacement parameters were not refined. Absorption correction was not necessary. Regina[67] weighting scheme was used in all cases.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 605567–605569. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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