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Diastereoselective synthesis of 1-alkyl-2,4,6-trioxoperhydropyrimidine-5-spiro-3′-(1′,2′,3′,4′-tetrahydroquinolines)

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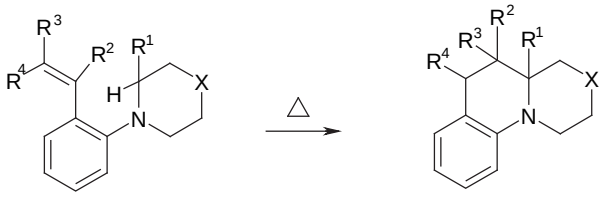
ABSTRACT

Knoevenagel products formed by the condensation of *N*-monoalkyl barbituric acids with *o*-tert-amino benzaldehydes undergo *tert*-amino effect reactions (T-reactions) yielding 1-alkyl-2,4,6-trioxoperhydropyrimidine-5-spiro-3′-(1′,2′,3′,4′-tetrahydroquinoline) derivatives as a mixture of (*S**,*S**)- and (*S**,*R**)-diastereomers. Mostly, the major diastereomer has the *S**,*S**-configuration. According to X-ray diffraction data in the solid form and NOE data in solution, diastereoselectivity of the T-reactions can be associated with the structure of the Knoevenagel products whose conformation is fixed by the strong intramolecular C—H···π interaction.

1. Introduction

The concept of the *tert*-amino effect formulated by Meth-Cohn and Suschitsky[1] refers to a great number of cyclization reactions involving *o*-substituted tertiary aromatic amines. One of the most important manifestations of the *tert*-amino effect includes the thermal isomerization of 2-vinyl-*N*,*N*-dialkylanilines leading to the annealed 1,2,3,4-tetrahydroquinoline systems (Scheme 1).[2,3] Despite the demanding conditions of the *tert*-amino effect reactions (T-reactions), the examples of diastereodirected and enantiodirected courses of isomerization have been described.[4,5]



Scheme 1. Thermal isomerization of 2-vinyl-*N*,*N*-dialkylanilines into 1,2-annelated 1,2,3,4-tetrahydroquinolines.

Recently, the synthetic potential of the *tert*-amino effect has been considerably extended due to the use of the cyclic β-dicarbonyl reagents, which allow T-reactions to proceed under surprisingly mild conditions.[6,7] Furthermore, most of 1,2,3,4-tetrahydroquinoline derivatives containing spirocyclic barbituric acid, Meldrum's acid, or cyclohexene-1,3-dione moieties were prepared in this fashion (Scheme 2).[6–10]

If an asymmetric carbon atom is present in the *tert*-amino group, the T-reactions may proceed diastereoselectively.[8,10] In such cases, the enantiomerically pure 1,2,3,4-tetrahydroquinolinic systems may be obtained from the chiral substrates (Scheme 2).[11]

In continuation of our previous studies on the stereochemical aspects of the *tert*-amino effect, herein we describe stereoselective T-reactions that result in the formation of compounds with two new chiral centers.

2. Results and discussion

Knoevenagel condensation of 1-methylbarbituric (**1a**) or 1-*tert*-butylbarbituric (**1k**) acids with 2-(*tert*-amino) benzaldehydes (**2a**–**j**) yields 1-alkyl-5-(2-(*tert*-amino)benzylidene)barbiturates (**3a**–**t**) as useful precursors for the syntheses of corresponding 5-spiro barbiturates (**4a**–**t**) (Scheme 3). In this case, the T-reaction leads to the formation of compounds with two new asymmetric centers. Hence, the final products **4a**–**t** may

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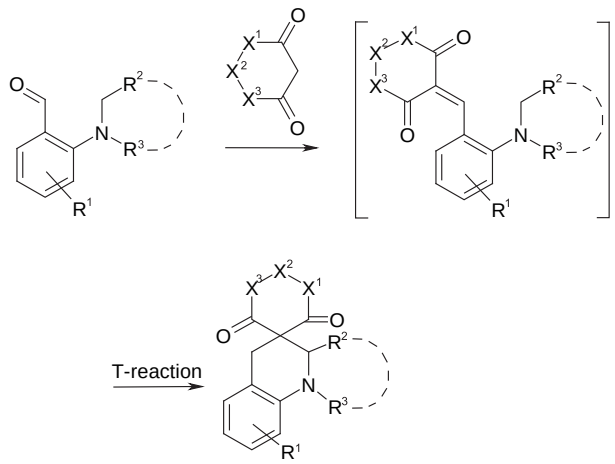
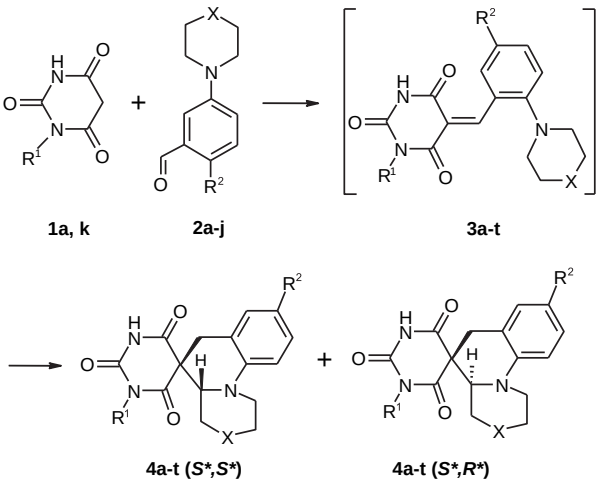


Scheme 2. Isomerization of 2-vinyl-*N*,*N*-dialkylanilines into 1,2-*a*nnelated 1,2,3,4-tetrahydroquinolines.



Scheme 3. The formation of 5-spiro barbiturates from 1-alkylbarbituric acids and 2-(*tert*-amino) benzaldehydes. R^1=Me (**a**–**j**), *t*-Bu (**k**–**t**); R^2=H (**a**–**c**, **f**, **h**, **k**–**m**, **p**, **r**), NO_2 (**d**, **e**, **g**, **i**, **j**, **n**, **o**, **q**, **s**, **t**); X=NPh (**a**, **k**), NMe (**b**, **i**, **l**, **s**), NCH_2Ph (**c**, **m**), —(**d**, **n**), CH_2 (**e**, **o**), CH_2CH_2 (**f**, **g**, **p**, **q**), O (**h**, **j**, **s**, **t**).

be obtained either as diastereomeric pairs with (*S**,*S**) or (*S**,*R**)-relative configuration of these centers, or as their mixture.

Condensation of acids **1a**,**k** with 2-(*N*-4-phenylpiperazino) benzaldehyde **2a** in 90%-ethanol afforded unstable Knoevenagel products **3a**,**k**, which undergo rapid isomerization into spirocyclic derivatives **4a**,**k** at room temperature. 1-Methyl-substituted derivative **4a** was obtained as a 9:1 mixture of (*S**,*S**)- and (*S**,*R**)-diastereomers, whereas 1-*tert*-butyl derivative **4k** was isolated almost quantitatively as the (*S**,*S**)-diastereomer (Table 1). The relative configurations of the major diastereomers of **4a** and **4k** were established by X-ray diffraction analysis (Fig. 1).

Table 1
Overall yield and diastereomeric ratio of spirocyclic derivatives **4a**–**t**

Starting reagents	R^1	R^2	X	Product	Method[a]	Overall yield, %	(*S**,*S**)/(*S**,*R**), %
1a+**2a**	Me	H	N–Ph	**4a**	A	87	90/10
1a+**2b**	Me	H	N–Me	**4b**	A	86	64/36
1a+**2c**	Me	H	N–CH_2Ph	**4c**	A	85	52/48
1a+**2d**	Me	NO_2	—	**4d**	A	84	53/47
1a+**2e**	Me	NO_2	CH_2	**4e**	A	71	100/0
1a+**2f**	Me	H	CH_2CH_2	**4f**	A	84	50/50
1a+**2g**	Me	NO_2	CH_2CH_2	**4g**	A	82	91/9
1a+**2h**	Me	H	O	**4h**	A	84	89/11
1a+**2i**	Me	NO_2	N–Me	**4i**	B	82	54/46
3j	Me	NO_2	O	**4j**	C	96	50/50
					D	100	74/26
1k+**2a**	*t*-Bu	H	N–Ph	**4k**	A	85	96/4
1k+**2b**	*t*-Bu	H	N–Me	**4l**	A	85	100/0
1k+**2c**	*t*-Bu	H	N–CH_2Ph	**4m**	A	85	93/7
1k+**2d**	*t*-Bu	NO_2	—	**4n**	A	80	78/22
1k+**2e**	*t*-Bu	NO_2	CH_2	**4o**	A	83	100/0
1k+**2f**	*t*-Bu	H	CH_2CH_2	**4p**	A	83	100/0
1k+**2g**	*t*-Bu	NO_2	CH_2CH_2	**4q**	A	74	100/0
1k+**2h**	*t*-Bu	H	O	**4r**	A	79	100/0
1k+**2i**	*t*-Bu	NO_2	N–Me	**4s**	B	65	100/0
3t	*t*-Bu	NO_2	O	**4t**	C	95	70/30

[a] See Experimental section.

Similarly, the condensation of acids **1a**,**k** with aldehydes **2b**–**h** is accompanied by rapid T-reaction leading directly to spirocyclic derivatives **4b**–**h**, **l**–**r** through the one-pot synthesis (method A, Table 1). The reaction rate is limited by the Knoevenagel condensation step, whereas highly reactive intermediates—1-alkyl-5-arylidene barbiturates **3a**–**h**, **l**–**r** formed in situ undergo immediate isomerization into the final spirocyclic systems.

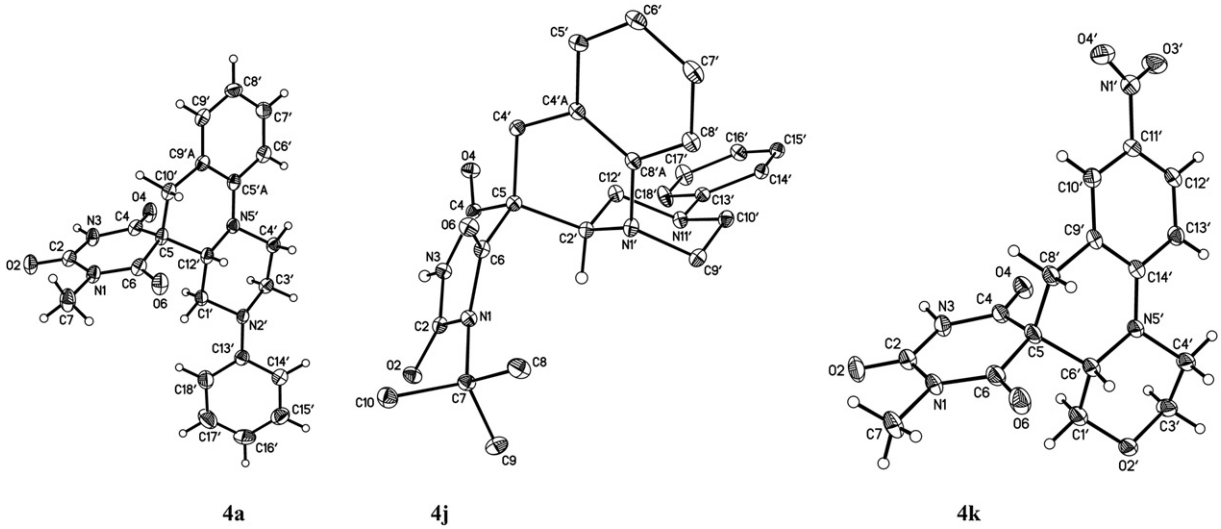


Figure 1. Molecular structures of **4a**, **4j**, and **4k**.

To distinguish the (*S**,*S**)- and (*S**,*R**)-diastereomers of **4a**, **4j**, and **4k** in their ^{1}H NMR spectra, we used the authentic samples of (*S**,*S**)-diastereomers, whose configuration was previously confirmed by X-ray diffraction study (Fig. 1). For other compounds, the proton signals of diastereomers **4** were identified by the characteristic chemical shifts of NH and NMe ($NCMe_3$) groups. Thus, for 5-spiro-derivatives of 1-methylbarbituric acid **4a** and **4j**, the NH signals from (*S**,*S**)-diastereomers (in DMSO-d_6) are observed at 11.40 and 11.55 ppm, whereas the NH signals from the corresponding (*S**,*R**)-isomers are shifted downfield by 0.19 ppm and observed at 11.59 and 11.74 ppm, respectively.

In contrast to aldehydes **2a**–**h**, 5-nitro-2-(4-*N*-methylpiperazino)benzaldehyde **2i** and 5-nitro-2-(*N*-morpholino)benzaldehyde **2j** react with acids **1a**,**k** to yield relatively stable 5-arylidene barbiturates (derivatives **3j**, **t** have been isolated). The isomerization of **3j** into **4j** in solution exhibited a lower diastereoselectivity, while heating of **3j** in the solid state (without solvent) yielded an excess of the (*S**,*S**)-diastereomer of **4j**. The latter was isolated and characterized by NMR spectroscopy and single-crystal X-ray analysis. As for the isomerization of 1-*tert*-butyl-5-arylidenebarbiturate **3t** into **4t**, diastereoselectivity of the T-reaction was moderate (Table 1).

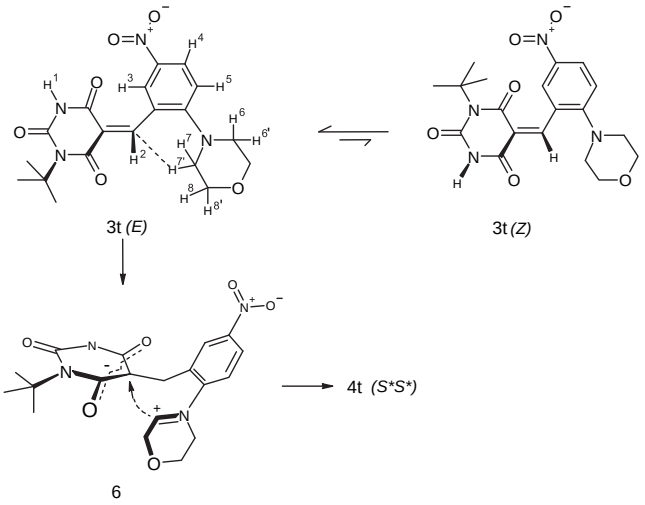
Thus, the isomerization of 1-*tert*-butyl-5-arylidene barbiturates **3k**–**t** predominantly results in the (*S**,*S**)-diastereomers of the corresponding spirocyclic **4**-compounds. The diastereodirected T-reaction was also observed for 1-methyl substituted substrates **3a**,**b**,**e**,**g**–**i** (for **3t** in solid phase), however, in the case of **3c**,**d**,**f**,**i**, diastereoselectivity was completely absent.

In order to rationalize the above trend toward the predominant (*S**,*S**)-diastereomer of **4**, we rigorously investigated the structure of Knoevenagel products (substrates of the T-reaction) using 1-*tert*-butyl-[5-nitro-2-(*N*-morpholino)benzylidene]barbituric acid **3t** and 1,3-dimethyl-[5-nitro-2-(*N*-morpholino)benzylidene]barbituric acid **5**[6] as model compounds.

Previously,[7] we reported that 5-(2-dimethylamino-5-nitrobenzylidene)barbituric acid exhibited a very short C–H···π(C=C) intramolecular contact between the hydrogen atom of one of the two methyl group of the amino substituent and the exocyclic carbon atom of the vinyl fragment, with the H···C interatomic distance of 2.34 Å. The X-ray structural data for compounds **3t** and **5** reveal the presence of similar contacts with the corresponding H···C interatomic distances of 2.26 and 2.35 Å, respectively (Fig. 2).

These observations are indicative of the very strong C–H···π interaction arising due to increased electron-withdrawing ability of the C=C vinyl bond in 5-benzylidene barbiturates. We proposed that such a strong C–H···π interaction can be used to explain the facile initiation of the T-reactions in compounds **3a**–**t** as well as in other 5-(2-dialkylaminobenzylidene) barbiturates and related compounds.

Isomerization of **3t** into the spirocyclic derivative **4t** (Scheme 4) proceeds via a zwitterionic intermediate **6** formed by uptake of 1,5-hydride. In this case, the C–H···π interaction observed in compound **3t** and its analogs (Fig. 2) both stabilizes the starting conformation, and creates the necessary prerequisites for the subsequent migration of the hydride from the NCH_2 group.



Scheme 4. Tautomeric *E*/*Z* equilibrium in compound **3t** and mechanism of the formation of the (*S**,*S**)-diastereomer **4t**.

In fact, the intramolecular C–H···π interaction can be regarded as the initial stage of the process: the abstraction of hydride ion by the polar C=C bond. Interestingly, this hydride uptake resembles the well-known reactions of nucleophilic addition of amines and OH^- to 5-benzylidene barbiturates.[12] The only difference is that in **3t** the reaction proceeds intramolecularly and the labile H^- ion acts as a nucleophile.

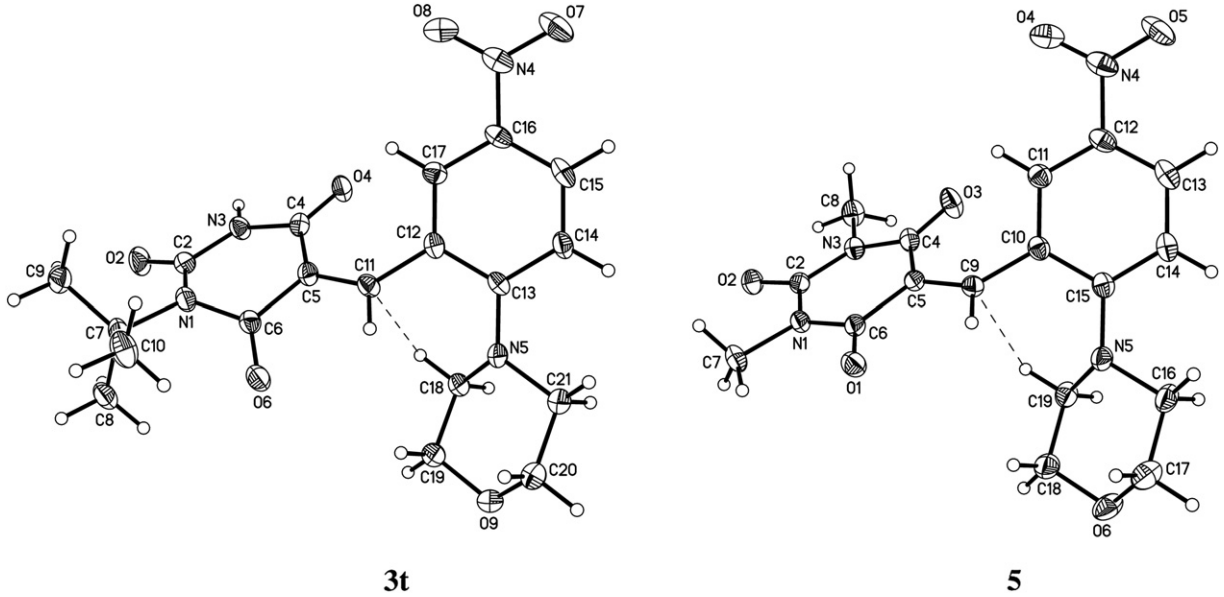


Figure 2. Molecular structure of compounds **3t** and **5**.

X-ray structural and ^{1}H NMR spectroscopy data for **3t** suggest that the crystals of **3t** are formed by the *E*-isomer only, whereas in solution, this compound is present as a mixture of *E*- and *Z*-isomers, the former being predominant. In the crystal, due to the strong C–H···π interaction, the molecule of **3t** (*E*) adopts the conformation in which the morpholine moiety is located as far from the *tert*-butylated nitrogen atom as possible (Fig. 2). Such a conformation of the starting molecule **3t**(*E*), in view of its subsequent disrotational isomerization via zwitterion **6**, favors the formation of (*S**,*S**)-diastereomer **4t** (Scheme 4). Accordingly, the starting conformation of **3t**(*Z*)-isomer should favor the formation of (*S**,*R**)-diastereomer **4t**.

The molecule of **3t**(*E*)-isomer (Fig. 2, Scheme 4) was confirmed, with the use of the Overhauser method, to retain its spatial structure both in solid state and in solution. During several hours after dissolution of **3t** in $CDCl_3$, the ^{1}H spectrum exhibited the following set of signals from **3t**(*E*)-isomer (500 MHz, δ, ppm, numeration of protons is given in Scheme 4): 1.70 (9H, s, $C(CH_3)_3$), 3.16 (4H, m, $N(CH_2)_2$), 3.91 (4H, m, $O(CH_2)_2$), 7.04 (1H, d, *J* 9.2 Hz, H^5), 8.00 (1H, s, NH), 8.26 (1H, dd, *J* 9.2, 2.4 Hz, H^4), 8.36 (1H, s,=CH), 8.80 (1H, d, *J* 2.4 Hz, H^3). ^{1}H–^{1}H NOE correlations for this compound (Table 2) are very close to theoretically expected values for the *E*-isomer, judging from the relevant H···H distances in its crystal structure.

Table 2
NOE correlations in (*E*)- and (*Z*)-isomers of compound **3t** in $CDCl_3$

Interacting protons in **3t**(*E*) and **3t**(*Z*)[a]	H–H distances in **3t**(*E*), Å[b]	NOE correlations, % for **3t**(*E*)	for **3t**(*Z*)
H^4–H^5	2.29	3	—[c]
H^5–H^6 and H^5–$H^{6'}$	2.15 and 2.68	100	100
H^2–$H^{7'}$	2.30	45	18
H^2–H^8	2.49	31	<5

[a] For numeration of protons, see Scheme 4.
[b] In solid state (from X-ray diffraction data).
[c] Obscured by signal from the *E* form.

If **3t**(*E*) is kept in $CDCl_3$ solution at 20 °C for prolonged periods of time, the ^{1}H NMR spectrum changes due to partial conversion of the starting compound into **3t**(*Z*)-isomer and exhibits the following set of signals: (500 MHz, δ, ppm, numeration of protons is given in Scheme 4): 1.71 (9H, s, $C(CH_3)_3$), 3.16 (4H, m, $N(CH_2)_2$), 3.91 (4H, m, $O(CH_2)_2$), 7.06 (1H, d, *J* 9.2 Hz, H^5), 8.14 (1H, s, NH), 8.28 (1H, dd, *J* 9.2, 2.4 Hz, H^4), 8.29 (1H, s,=CH), 8.43 (1H, d, *J* 2.4 Hz, H^3). The *E*/*Z*-isomerization around the C=C bond is reversible: equilibrium in the system was achieved in 10 days. According to our ^{1}H NMR data, the equilibrium mixture contained 65% **3t**(*E*)- and 35% **3t**(*Z*)-isomer.

The NOE correlations (Table 2) show that the $H^2\cdots H^{7'}$ distance in **3t**(*E*)-isomer is within 2.30–2.40 Å, whereas it increases up to 2.70–2.80 Å in **3t**(*Z*)-isomer; therefore, the **3t**(*E*)→**3t**(*Z*) transformation is accompanied by significant weakening of a remarkable C–H···π interaction.

Based on the above considerations we conclude that the more stable **3t**(*E*)-isomer enters into the T-reaction more readily because its starting conformation is more favorable for the hydride uptake as compared to that of the **3t**(*Z*)-isomer. The predisposition of **3t**(*E*)-isomer for conversion into (*S**,*S**)-diastereomer **4t** provides a logical explanation for the predominance of the latter in the products of the T-reaction.

3. Conclusion

We have rationalized the tendency of 1-monoalkyl 5-(2-dialkylaminobenzylidene)barbituric acids **3** to isomerize into products **4** with the predominant (*S**,*S**)-configuration. The C–H···π interaction in the intermediates **3** seems to be a crucial factor of the T-reaction that involves a hydride uptake and determines the stereochemical ratio of the formed products **4a**–**t**. The stronger C–H···π interaction occurs in **3**(*E*)-isomers, and facilitates the predominant formation of (*S**,*S**)-diastereomers of **4**.

It is interesting to note that, for slowly isomerizing substrates **3j** and **3t**, diastereoselectivity of the T-reactions is low, whereas their unstable and highly reactive analogs **3a**–**h**, **k**–**r** mostly react stereoselectively yielding the (*S**,*S**)-diastereomers **4** in quantitative yield.

4. Experimental section

4.1. General

The ^{1}H and ^{13}C NMR spectra were recorded on a AM-500 Bruker spectrometer (500 and 200 MHz, respectively). The purity of synthesized compounds was determined by elemental analysis and ^{1}H NMR spectroscopy. The relative amounts of (*S**,*S**)- and (*S**,*R**)-diastereomers in products (**4a**–**t**) were derived from the intensity of proton signals of NH groups (in ^{1}H NMR spectra), at the integration accuracy better than 2%. The relevant data are collected in Table 1.

Starting aldehydes **2a**–**c** were prepared from *o*-fluorobenzaldehyde and corresponding amines by use of the method described in,[2] while derivatives **2f**, **2h** in a similar way following the methods.[3,5] Aldehydes **2d**, **2e**, **2g**, **2i**, **2j** were prepared from 2-chloro-5-nitrobenzaldehyde and corresponding amines by method.[6] Compound **5** was synthesized from aldehyde **2j** and 1,3-dimethylbarbituric acid by method.[6]

Crystals of compounds **3t**, **4a**, **4j**, **4k**, and **5** suitable for X-ray structural analysis were grown from water-ethanol solutions.

4.2. X-ray structure determination

Data for **3t**, **4a**, **4j**, **4k**, and **5** were collected on a Bruker SMART 1 K CCD diffractometer (λMo $K\alpha$-radiation, graphite monochromator, ω and φ scan mode). For details, see Table 3. The structures were determined by direct methods and refined by full-matrix least squares technique on F^2 with anisotropic displacement parameters for non-hydrogen atoms. The hydrogen atoms of the amino-groups in **3t** were objectively located in the difference Fourier map and refined isotropically. The hydrogen atoms of the amino-groups in **4a** and **4j** were objectively located in the difference Fourier map and refined with fixed positional and isotropic displacement parameters. The other hydrogen atoms in **3t**, **4a**, and **4j** and all hydrogen atoms in **4k** and **5** were placed in calculated positions and refined in riding model with fixed isotropic displacement parameters [$U_{iso}(H)$=1.5$U_{eq}(C)$ for the CH_3 groups and $U_{iso}(H)$=1.2$U_{eq}(C)$ for the other groups]. All calculations were carried out using the SHELXTL program.[13] Crystallographic data for **3t**, **4a**, **4j**, **4k**, and **5** have been deposited with the Cambridge Crystallographic Data Center, CCDC 665417-665421. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk).

4.3. General method A—the procedure for synthesis of 5-spiro barbiturates 4a–h, k–r (Table 1)

*4.3.1. 1-Methyl-2,4,6-trioxospiro(perhydropyrimidino-5,5′-(3′-phenyl-1′,2′,3′,3a′,4′,5′-hexahydro-1H-pyrazino[1,2-a]quinoline)) (**4a**).* A solution of 5 mmol (0.71 g) acid **1a** in 50% ethanol (10 ml) was added to a solution of 5 mmol (1.32 g) aldehyde **2a** in 90% ethanol (20 ml) at 50 °C, and the reaction mixture was stirred for 5 min. After staying at room temperature for 1 h, water (10 ml) was added. The precipitated colorless crystals were separated, washed with 50% ethanol, and air dried to give a mixture of (*S**,*S**)- and (*S**,*R**)-diastereomers **4a**; δ_H (500 MHz, DMSO-d_6) 11.59 and 11.40

Table 3
Crystallographic data for **3t**, **4a**, **4j**, **4k**, and **5**

Compound	**3t**	**4a**	**4k**	**4j**	**5**
Empirical formula	$C_{19}H_{22}N_4O_6$	$C_{22}H_{22}N_4O_3$	$C_{25}H_{28}N_4O_3$	$C_{16}H_{16}N_4O_6$	$C_{17}H_{18}N_4O_6$
Fw	402.41	390.44	432.51	360.33	374.35
T, K	120 (2)	120 (2)	120 (2)	120 (2)	120 (2)
Crystal size, mm	0.24×0.21×0.15	0.30×0.30×0.05	0.21×0.18×0.12	0.24×0.21×0.18	0.24×0.21×0.18
Crystal system	Triclinic	Orthorhombic	Orthorhombic	Monoclinic	Monoclinic
Space group	P-1	$Pca2_1$	Pbca	$P2_1/c$	$P2_1/n$
a, Å	7.697 (3)	15.718 (3)	12.376 (4)	9.700 (3)	7.3557 (8)
b, Å	11.824 (5)	16.583 (4)	17.568 (5)	11.588 (4)	8.5607 (10)
c, Å	12.033 (5)	7.3072 (16)	20.348 (7)	13.849 (4)	26.757 (3)
α, deg	63.323 (8)	90	90	90	90
β, deg	84.427 (8)	90	90	99.471(7)	95.215 (5)
γ, deg	71.561 (8)	90	90	90	90
V, Å^3	927.0 (7)	1904.6 (7)	4424 (2)	1535.6 (8)	1677.9 (3)
Z	2	4	8	4	4
d_c, g×cm^{-3}	1.442	1.362	1.299	1.559	1.482
F (000)	424	824	1840	752	784
μ, mm^{-1}	0.109	0.093	0.087	0.122	0.114
$2\theta_{max}$, deg	50	56	50	52	56
Index range	−9<=*h*<=9 −14<=*k*<=14 −13<=*l*<=14	−20<=*h*<=20 −21<=*k*<=21 −9<=*l*<=9	−14<=*h*<=14 −18<=*k*<=20 −24<=*l*<=24	−11<=*h*<=11 −14<=*k*<=14 −17<=*l*<=15	−9<=*h*<=9 −11<=*k*<=11 −35<=*l*<=34
No. of rflns collected	6521	18,733	22,758	8783	16,774
No. of unique rflns	3188 (R_{int}=0.064)	4571 (R_{int}=0.053)	3890 (R_{int}=0.077)	3002 (R_{int}=0.032)	4033 (R_{int}=0.026)
No. of rflns with $I>2\sigma(I)$	1762	3342	2038	1948	3020
Data/restraints/parameters	3188/0/266	4571/1/263	3890/0/289	3002/0/236	4033/0/246
*R*1; *wR*2 ($I>2\sigma(I)$)	0.074; 0.159	0.054; 0.114	0.067; 0.132	0.053; 0.124	0.046; 0.102
*R*1; *wR*2 (all data)	0.132; 0.179	0.074; 0.122	0.124; 0.146	0.077; 0.137	0.062; 0.108
GOF on F^2	1.015	1.004	1.036	1.002	1.002
T_{min}; T_{max}	0.976; 0.988	0.969; 0.996	0.982; 0.990	0.970; 0.980	0.970; 0.983

(0.1H+0.9H, s+s, N*H* (*S**,*R** and *S**,*S**)), 7.18 (2H, dd, *J* 7.4 Hz, H_{arom}), 7.04 (1H, dd, *J* 7.4 Hz, H_{arom}), 6.94 (1H, d, *J* 6.9 Hz, H_{arom}), 6.87 (1H, d, *J* 7.9 Hz, H_{arom}), 6.82 (2H, dd, *J* 7.5 Hz, H_{arom}), 6.76 (1H, dd, *J* 6.8 Hz, H_{arom}), 6.64 (1H, dd, *J* 6.9 Hz, H_{arom}), 4.06 and 2.70 (1H+1H, m+m, *J* 10.7 Hz, NCH_aH_b), 3.74 (1H, dd, *J* 9.5, 3.1 Hz, NC*H*), 3.60 and 3.38 (1H+1H, m, *J* 10.6 Hz, NCH_aH_b), 3.24 and 3.08 (0.3H+2.7H, s+s, N*Me* (*S**,*R** and *S**,*S**)), 3.27 and 3.18 (2H, d+d, *J* 16.6 Hz, CH_aH_bAr), 3.17 and 2.96 (1H+1H, m+m, *J* 11.0 Hz, NCH_aH_bCH).

The pure (*S**,*S**)-diastereomer of **4a** was obtained by recrystallization from 10:1 ethanol/DMF solution as colorless plate-like crystals, mp 239–242 °C; [found: C 67.44; H 5.60; N 14.19. $C_{22}H_{22}N_4O_3$ requires C 67.68; H 5.68; N 14.35%]; δ_C (200 MHz, DMSO-d_6) 170.72, 168.08, 150.56, 150.38, 144.11, 129.22, 128.61, 126.74, 121.39, 119.56, 117.93, 115.60, 113.17, 59.24, 50.37, 48.33, 47.62, 46.31, 33.48, 27.48.

*4.3.2. 1-Methyl-2,4,6-trioxospiro(perhydropyrimidino-5,5′-(3′-methyl-1′,2′,3′,3a′,4′,5′-hexahydro-1H-pyrazino[1,2-a]quinoline)) (**4b**).* Mixture of (*S**,*S**)- and (*S**,*R**)-diastereomers. Colorless powder, mp 213–216 °C; [found: C 62.31; H 5.69; N 16.93. $C_{17}H_{20}N_4O_3$ requires C 62.18; H 6.14; N 17.06%]; δ_H (500 MHz, DMSO-d_6) 11.61 and 11.49 (0.36H+0.64H, s+s, N*H* (*S**,*R** and *S**,*S**)), 7.01 (1H, dd, *J* 7.9 Hz, H_{arom}), 6.92 (1H, d, *J* 8.9 Hz, H_{arom}), 6.82 (1H, m, H_{arom}), 6.64 (1H, m, H_{arom}), 3.88 (1H, m, NC*H*), 3.39 and 2.74 (2H, m+m, NCH_aH_b), 3.26 and 3.09 (1H+1H, d+d, *J* 16.5 Hz, CH_aH_bAr), 3.24 (3H, s, N*Me*), 2.90 and 2.09 (1H+1H, m+m, NCH_aH_b), 2.55 and 1.79 (1H+1H, m, *J* 9.5 Hz, AB-system, NCH_2), 2.21 (3H, s, N*Me*); δ_C (200 MHz, DMSO-d_6) 172.20, 171.64, 168.17, 167.53, 150,03, 141.79, 129.12, 126.80, 122.05, 117.98, 113.76, 59.25, 58.79, 50.73, 50.46, 47.62, 47.48, 46.60, 46.44, 45.76, 45.65, 33.63, 33.48, 28.04, 27.41.

*4.3.3. 1-Methyl-2,4,6-trioxospiro(perhydropyrimidino-5,5′-(3′-benzyl-1′,2′,3′,3a′,4′,5′-hexahydro-1H-pyrazino[1,2-a]quinoline)) (**4c**).* Mixture of (*S**,*S**)- and (*S**,*R**)-diastereomers. Colorless acicular crystal, mp 225–229 °C; [found: C 68.42; H 6.01; N 13.79. $C_{23}H_{24}N_4O_3$ requires C 68.30; H 5.98; N 13.85%]; δ_H (500 MHz, DMSO-d_6) 11.60 and 11.41 (0.48H+0.52H, s+s, N*H* (*S**,*R** and *S**, *S**)), 7.33–7.20 (5H, m, *Ph*), 6.99 (1H, m, H_{arom}), 6.91 (1H, m, H_{arom}), 6.80 (1H, m, H_{arom}), 6.64 (1H, m, H_{arom}), 3.81 (1H, dd, *J* 9.5, 3.9 Hz, NC*H*), 3.54–3.30 (3H, m, NCH_2Ar and CH*H*), 3.26 and 3.09 (1H+1H, d+d, *J* 16.9 Hz, CH_aH_bAr), 3.19 and 3.11 (1.59H+1.41H, s+s, N*Me* (*S**,*R** and *S**,*S**)), 2.08–2.36 (4H, m, 2NCH_2), 1.93 (1H, m, NC*H*H).

*4.3.4. 1-Methyl-2,4,6-trioxospiro(perhydropyrimidino-5,5′-(7′-nitro-1′,2′,3′,3a′,4′,5′-hexahydropyrrolo[1,2-a]quinoline)) (**4d**).* Mixture of (*S**,*S**)- and (*S**,*R**)-diastereomers. Yellow crystals, mp 301–305 °C (decomp.); [found: C 55.57; H 4.77; N 16.09. $C_{16}H_{16}N_4O_5$ requires C 55.81; H 4.68; N 16.27%]; δ_H (500 MHz, DMSO-d_6) 11.78 and 11.51 (0.47H+0.53H, s+s, NH (*S**,*R** and *S**,*S**)), 8.92 (1H, d, *J* 8.8 Hz, H_{arom}), 7.83 (1H, d, *J* 2.4 Hz, H_{arom}), 6.55 (1H, dd, *J* 8.8, 2.4 Hz, H_{arom}), 3.89 (1H, m, NCH), 3.70 (1H, t, *J* 11.1 Hz, NCH*H*-eq), 3.37 (3H, m, NC*H*H+CH_2Ar), 3.22 and 3.06 (1.41H+1.59H, s+s, N*Me* (*S**,*R** and *S**,*S**)), 2.20–1.95 (3H, m, CH_2+CH*H*-eq), 1.53 (1H, m, CH*H*-ax).

4.3.5. (S,S*)-1-Methyl-2,4,6-trioxospiro(perhydropyrimidino-5,5′-(8′-nitro-1′,2′,3′,3a′,4′,5′-hexahydropyrido[1,2-a]quinoline)) (**4e**).* Yellow acicular crystals, mp 310–312 °C (decomp.); [found, C 56.74; H 5.21; N 15.50. $C_{17}H_{18}N_4O_5$ requires C 56.98; H 5.06; N 15.63%]; δ_H (500 MHz, DMSO-d_6) 11.48 (1H, s, N*H*), 7.90 (1H, dd, *J* 9.2, 2.3 Hz, H_{arom}), 7.85 (1H, d, *J* 2.3 Hz, H_{arom}), 6.91 (1H, d, *J* 9.2 Hz, H_{arom}), 4.21 (1H, dd, *J* 9.9, 4.6 Hz, NC*H*), 3.73 and 3.08 (1H+1H, d+d, *J* 12.5 Hz, NCH_aH_b), 3.39 and 3.05 (1H+1H, d+d, *J* 17.2 Hz, CH_aH-$_b$Ar), 3.12 (3H, s, NCH_3), 1.84–1.23 (6H, m, 3CH_2); δ_C (200 MHz, DMSO-d_6) 170.22, 168.36, 150,66, 149.60, 136.55, 124.20, 123.46, 121.77, 111.60, 60.76, 51.94, 48.58, 29.03, 27.88, 26.89, 23.86, 23.28.

*4.3.6. 1-Methyl-2,4,6-trioxospiro(perhydropyrimidino-5,5′-(5′,6′,6a′,7′,8′,9′,10′,11′-octahydroazepino[1,2-a]quinoline)) (**4f**).* Mixture of (*S**,*S**)- and (*S**,*R**)-diastereomers. Colorless powder, mp 229–233 °C; [found: C 66.19; H 6.56; N 12.68. $C_{18}H_{21}N_3O_3$

requires C 66.04; H 6.47; N 12.84%]; δ_H (500 MHz, DMSO-d_6) 11.37 and 11.25 (0.5H+0.5H, s+s, N*H* (*S**,*S** and *S**,*R**)), 6.98 (2H, m, H_{arom}), 6.60 (2H, m, H_{arom}), 3.60 (1H, m, NC*H*), 3.59 and 3.22 (1H+1H, m+m, NCH_aH_b), 3.35 and 3.01 (1H+1H, d+d, *J* 17.4 Hz, CH_aH_bAr), 3.17 and 3.11 (1.5H+1.5H, s+s, N*Me* (*S**,*S** and *S**,*R**)), 1.40–1.95 (8H, m, 4CH_2).

*4.3.7. 1-Methyl-2,4,6-trioxospiro(perhydropyrimidino-5,5′-(3′-nitro-5′,6′,6a′,7′,8′,9′,10′,11′-octahydroazepino[1,2-a]quinoline)) (**4g**).* Mixture of (*S**,*S**)- and (*S**,*R**)-diastereomers. Yellow powder, mp 299–301 °C; [found: C 58.00; H 5.53; N 14.94. $C_{18}H_{20}N_4O_5$ requires C 58.06; H 5.41; N 15.05%]; δ_H (500 MHz, DMSO-d_6) 11.41 and 11.25 (0.91H+0.09H, s+s, N*H* (*S**,*S** and *S**,*R**)), 7.94 (1H, d, *J* 2.6 Hz, H_{arom}), 6.98 (2H, m, H_{arom}), 6.66 (1H, d, *J* 9.0 Hz, H_{arom}), 3.95 (1H, dd, *J* 8.0, 4.6 Hz, NC*H*), 3.87 and 3.25 (1H+1H, m+m, NCH_aH_b), 3.49 and 2.96 (1H+1H, d+d, *J* 17.7 Hz, CH_aH_bAr), 3.14 and 3.06 (2.73H+0.27H, s+s, N*Me* (*S**,*S** and *S**,*R**)), 1.33–1.99 (8H, m, 4CH_2); δ_C (200 MHz, DMSO-d_6) 170.53, 168.67, 150,45, 149.81, 136.13, 123.80, 123.04, 121.23, 112.36, 60.15, 51.28, 48.11, 29.10, 27.82, 27.19, 24.22, 23.24, 22.90.

*4.3.8. 1-Methyl-2,4,6-trioxospiro(perhydropyrimidino-5,5′-(1′,3′,4′,9′,10′,10a′-hexahydro-2-oxa-4a-phenanthrene)) (**4h**).* Mixture of (*S**,*S**)- and (*S**,*R**)-diastereomers. Colorless acicular crystals, mp 224–226 °C; [found: C 60.89; H 5.46; N 13.31. $C_{16}H_{17}N_3O_4$ requires C 60.94; H 5.43; N 13.33%]; δ_H (500 MHz, DMSO-d_6) 11.64 and 11.45 (0.11H+0.89H, s+s, N*H* (*S**,*S** and *S**, *R**)), 7.04 (1H, dd, *J* 7.7 Hz, H_{arom}), 6.94 (1H, d, *J* 7.8 Hz, H_{arom}), 6.83 (1H, d, *J* 7.7 Hz, H_{arom}), 6.67 (1H, dd, *J* 7.8 Hz, H_{arom}), 3.74 (1H, dd, *J* 9.4, 4.8 Hz, NC*H*), 3.87+3.79+3.41+3.32+3.10+3.04 (1H+1H+1H+1H+1H+1H, m, NCH_aH_b+2OCH_aH_b), 3.32 and 2.99 (1H+1H, d+d, *J* 17.2 Hz, CH_aH_bAr), 3.28 and 3.19 (0.33H+2.67H, s+s, NCH_3 (*S**,*R** and *S**,*S**)); δ_C (200 MHz, DMSO-d_6) 171.14, 167.96, 150.33, 142.22, 129.40, 126.56, 122.87, 118.64, 113.41, 64.98, 63.25, 59.72, 52.47, 48.39, 28.82, 27.51.

*4.3.9. 1-tert-Butyl-2,4,6-trioxospiro(perhydropyrimidino-5,5′-(3′-phenyl-1′,2′,3′,3a′,4′,5′-hexahydro-1H-pyrazino[1,2-a]quinoline)) (**4k**).* Mixture of (*S**,*S**)- and (*S**,*R**)-diastereomers; δ_H (500 MHz, DMSO-d_6) 11.30 and 11.18 (0.04H+0.96H, s+s, N*H* (*S**,*R** and *S**,*S**)), 7.17 (2H, dd, *J* 8.3, 7.2 Hz, H_{arom}), 7.04 (2H, m, H_{arom}), 6.90 (1H, d, *J* 8.3 Hz, H_{arom}), 6.81 (2H, d, *J* 8.2 Hz, H_{arom}), 6.76 (1H, t, *J* 7.2 Hz, H_{arom}), 6.69 (1H, t, *J* 7.2 Hz, H_{arom}), 4.23 and 3.27 (1H+1H, m, *J* 14.3 Hz, NCH_aH_b), 3.99 (1H, dd, *J* 10.7, 2.9 Hz, NC*H*), 3.42 and 2.94 (1H+1H, d, *J* 16.7 Hz, CH_aH_bAr), 3.40 and 3.26 (1H+1H, m, *J* 12.0 Hz, NCH_aH_b), 2.81 and 2.61 (1H+1H, m, *J* 11.4 Hz, NCH_aH_b), 1.53 and 1.48 (8.6H+0.4H, s+s, *t-Bu* (*S**,*S** and *S**,*R**)).

The pure (*S**,*S**)-diastereomer **4k** was obtained by recrystallization from ethanol as colorless acicular crystals, mp 226–227 °C; [found, C 69.60; H 6.41; N 12.73. $C_{25}H_{28}N_4O_3$ requires C 69.42; H 6.53; N 12.95%]; δ_C (200 MHz, DMSO-d_6) 172.36, 167.48, 150.79, 149.73, 141.60, 129.18, 126.91, 122.10, 119.81, 118.29, 115.79, 114.04, 59.89, 59.59, 53.80, 47.72, 46.74, 44.81, 28.77, 26.69.

4.3.10. (S,S*)-1-tert-Butyl-2,4,6-trioxospiro(perhydropyrimidino-5,5′-(3′-methyl-1′,2′,3′,3a′,4′,5′-hexhydro-1H-pyrazino[1,2-a]quinoline)) (**4l**).* Colorless acicular crystals, mp 219–221 °C; [found, C 64.99; H 7.15; N 15.06. $C_{20}H_{26}N_4O_3$ requires C 64.85; H 7.07; N 15.12%]; δ_H (500 MHz, DMSO-d_6) 11.17 (1H, s, NH), 7.01 (2H, m, H_{arom}), 6.81 (1H, dd, *J* 7.6, 5.2 Hz, H_{arom}), 6.67 (1H, dd, *J* 7.1, 4.9 Hz, H_{arom}), 4.06 and 3.08 (1H+1H, dd+dd, *J* 14.7 Hz, NCH_aH_b), 3.76 (1H, dd, *J* 9.7 Hz, NC*H*), 3.22 and 2.85 (1H+1H, d+d, *J* 17.1 Hz, CH_aH_bAr), 2.49 and 2.42 (1H+1H, m, NCH_aH_b), 2.14 (3H, s, N*Me*), 2.04 and 1.84 (1H+1H, dd+dd, *J* 11.3 Hz, NCH_aH_b), 1.49 (9H, s, *t-Bu*); δ_C (200 MHz, DMSO-d_6) 172.51, 167.44, 149.78, 141.83, 129.16, 126.85, 122.06, 118.08, 113.94, 60.83, 59.51, 53.83, 52.53, 50.40, 48.14, 45.75, 28.72, 25.99.

*4.3.11. 1-tert-Butyl-2,4,6-trioxospiro(perhydropyrimidino-5,5′-(3′-benzyl-1′,2′,3′,3a′,4′,5′-hexahydro-1H-pyrazino[1,2-a]quinoline)) (**4m**).* Mixture of (*S**,*S**)- and (*S**,*R**)-diastereomers; δ_H (500 MHz, $CDCl_3$) 8.44 and 7.73 (0.07H+0.93H, s+s, N*H* (*S**,*R** and *S**,*S**)), 7.17 (2H, dd, *J* 8.3, 7.2 Hz, H_{arom}), 7.04 (2H, m, H_{arom}), 6.90 (1H, d, *J* 8.3 Hz, H_{arom}), 3.92 (1H, dd, *J* 10.1, 5.4 Hz, NC*H*), 4.00 and 3.21 (1H+1H, m+m, *J* 14.0 Hz, NCH_aH_b), 3.66 and 3.26 (1H+1H, dd+dd, *J* 12.5 Hz, NCH_aH_b), 2.73 and 2.59 (1H+1H, dd, *J* 11.1, 5.9 Hz, NCH_aH_b), 1.51 and 1.47 (8.37H+0.63H, s+s, *t-Bu* (*S**,*S** and *S**,*R**)).

The pure (*S**,*S**)-diastereomer **4m** was isolated by recrystallization from ethanol as colorless acicular crystals, mp 225 °C (decomp.); [found, C 70.11; H 6.84; N 16.39. $C_{26}H_{30}N_4O_3$ requires C 69.93; H 6.77; N 12.55%]; δ_C (200 MHz, DMSO-d_6) 172.35, 167.43, 149.77, 142.20, 137.67, 129.05, 128.33, 127.18, 126.82, 122.14, 118.25, 118.16, 113.84, 62.27, 60.91, 59.64, 53.70, 51.10, 49.05, 48.08, 28.74, 26.95.

*4.3.12. 1-tert-Butyl-2,4,6-trioxospiro(perhydropyrimidino-5,5′-(7′-nitro-1′,2′,3′,3a′,4′,5′-hexahydropyrrolo[1,2-a]quinoline)) (**4n**).* Mixture of (*S**,*S**)- and (*S**,*R**)-diastereomers. Yellow acicular crystals, mp 240 °C (decomp.); [found: C 58.97; H 5.80; N 14.39. $C_{19}H_{22}N_4O_5$ requires C 59.06; H 5.74; N 14.50%]; δ_H (500 MHz, DMSO-d_6) 11.42 and 11.20 (0.22H+0.78H, s+s, N*H* (*S**,*R** and *S**,*S**)), 7.91 (2H, m, H_{arom}), 6.50 (1H, m, H_{arom}), 3.98 and 3.81 (0.22H+0.78H, dd+dd, *J* 12.2 Hz, NC*H* (*S**,*R** and *S**,*S**)), 3.70 (1H, m, NCH*H*-eq), 3.29 (3H, m, NC*H*H+CH_2Ar), 1.98–2.22 (3H, m, CH_2+CH*H*-eq), 1.56 (1H, m, CH*H*-ач), 1.54 and 1.36 (7.03+1.97H, s+s, *t-Bu*, *S**,*S** and *S**,*R**); δ_C (200 MHz, DMSO-d_6) 172.67, 166.96, 149.64, 148.59, 137.21, 124.68, 123.46, 122.22, 112.34, 62.38, 59.50, 54.25, 49.48, 28.67, 26.00, 25.31, 24.20.

4.3.13. (S,S*)-1-tert-Butyl-2,4,6-trioxospiro(perhydropyrimidino-5,5′-(8′-nitro-1′,2′,3′,3a′,4′,5′-hexahydropyrido[1,2-a]quinoline)) (**4o**).* Yellow acicular crystals, mp 244 °C (decomp.); [found: C 60.06, H 5.98, N 13.91. $C_{20}H_{24}N_4O_5$ requires C 59.99, H 6.04, N 13.99%]; δ_H (500 MHz, DMSO-d_6) 11.17 (1H, s, N*H*), 7.98 (1H, d, *J* 2.2 Hz, H_{arom}), 7.89 (1H, dd, J^1 9.2, 2.2 Hz, H_{arom}), 6.92 (1H, d, *J* 9.2 Hz, H_{arom}), 4.21 (1H, dd, *J* 9.8, 5.0 Hz, NC*H*), 3.92 and 3.11 (1H+1H, m+m, *J* 12.2 Hz, NCH_aH_b), 3.32 and 2.94 (1H+1H, d+d, *J* 17.0 Hz, CH_aH_bAr), 1.49 (9H, s, *t-Bu*), 1.87–1.25 (6H, m, 3CH_2); δ_C (200 MHz, DMSO-d_6) 171.53, 168.01, 150,12, 149.50, 136.08, 124.96, 123.23, 122.15, 112.27, 60.94, 52.58, 51.90, 48.61, 29.34, 28.52, 26.66, 24.04, 23.75.

4.3.14. (S,S*)-1-tert-Butyl-2,4,6-trioxospiro(perhydropyrimidino-5,5′-(5′,6′,6a′,7′,8′,9′,10′,11′-octahydroazepino[1,2-a]quinoline)) (**4p**).* Colorless acicular crystals, mp 222–223 °C; [found: C 68.04, H 7.45, N 11.28. $C_{21}H_{27}N_3O_3$ requires C 68.27, H 7.37, N 11.37%]; δ_H (500 MHz, DMSO-d_6) 11.92 (1H, s, N*H*), 7.03 (1H, d, *J* 8.4 Hz, H_{arom}), 6.94 (1H, dd, *J* 8.4, 7.0 Hz, H_{arom}), 6.59 (1H, dd, *J* 8.4, 7.0 Hz, H_{arom}), 6.49 (1H, d, *J* 8.4 Hz, H_{arom}), 3.88 and 3.10 (1H+1H, m+m, *J* 14.0 Hz, NCH_aH_b), 3.82 (1H, dd, *J* 9.6, 6.0 Hz, NC*H*), 3.41 and 2.82 (1H+1H, d+d, *J* 16.8 Hz, CH_aH_bAr), 2.13 (1H, m, C*H*H), 1.64–1.30 (7H, m, 3CH_2+CH*H*), 1.50 (9H, s, *t-Bu*); δ_C (200 MHz, DMSO-d_6) 172.89, 168.00, 149.96, 142.06, 128.85, 126.64, 119.36, 116.38, 110.82, 64.42, 59.42, 55.25, 49.75, 30.00, 28.79, 26.58, 24.92, 24.87, 24.44.

4.3.15. (S,S*)-1-tert-Butyl-2,4,6-trioxospiro(perhydro-pyrimidino-5,5′-(3′-nitro-5′,6′,6a′,7′,8′,9′,10′,11′-octahydro-azepino[1,2-a]quinoline)) (**4q**).* Yellow acicular crystals, mp 256 °C (decomp.); [found: C 60.98, H 6.40, N 13.42. $C_{21}H_{26}N_4O_5$ requires C 60.86, H 6.32, N 13.52%]; δ_H (500 MHz, DMSO-d_6) 10.94 (1H, s, N*H*), 7.94 (1H, d, *J*

2.5 Hz, H_{arom}), 7.89 (1H, dd, *J* 8.3, 2.5 Hz, H_{arom}), 6.65 (1H, d, *J* 8.3 Hz, H_{arom}), 3.97 and 3.36 (1H+1H, m+m, NCH_aH_b), 3.94 (1H, dd, *J* 9.5, 5.0 Hz, NC*H*), 3.42 and 2.86 (1H+1H, d+d, *J* 17.4 Hz, CH_aH_bAr), 1.99 (1H, m, C*H*H), 1.60 (9H, s, *t-Bu*), 1.57–1.30 (7H, m, 3CH_2+CH*H*); δ_C (200 MHz, DMSO-d_6) 171.96, 166.62, 150.23, 148.16, 136.40, 124.08, 123.19, 121.74, 112.97, 61.15, 59.48, 54.11, 49.23, 29.65, 28.67, 26.49, 24.88, 24.62, 24.21.

4.3.16. (S,S*)-1-tert-Butyl-2,4,6-trioxospiro(perhydro-pyrimidino-5,5′-(1′,3′,4′,9′,10′,10a′-hexahydro-2-oxa-4a-phenanthrene)) (**4r**).* Colorless acicular crystals, mp 198–199 °C; [found: C 63.97, H 6.56, N 11.69. $C_{19}H_{23}N_3O_4$ requires C 63.85, H 6.49, N 11.76%]; δ_H (500 MHz, DMSO-d_6) 11.13 (1H, s, N*H*), 7.03 (2H, m, H_{arom}), 6.79 (1H, d, *J* 8.3 Hz, H_{arom}), 6.68 (1H, dd, *J* 7.5 Hz, H_{arom}), 3.95+3.83+3.54+3.52+3.34+3.19 (1H+1H+1H+1H+1H+1H, m, NCH_2+2 °CH_2), 3.64 (1H, dd, *J* 7.9, 5.0 Hz, NC*H*), 3.20 and 2.92 (1H+1H, d+d, *J* 16.5 Hz, CH_aH_bAr), 1.53 (9H, s, *t-Bu*); δ_C (200 MHz, DMSO-d_6) 172.20, 167.26, 149.68, 142.27, 129.05, 126.96, 121.98, 118.21, 113.78, 65.00, 63.42, 60.22, 59.72, 52.83, 48.83, 28.72, 28.10.

4.4. General method B—the procedure for synthesis of 5-spiro barbiturates 4i,s (Table 1)

*4.4.1. 1-Methyl-2,4,6-trioxospiro(perhydropyrimidino-5,5′-(3′-methyl-8′-nitro-1′,2′,3′,3a′,4′,5′-hexahydro-1H-pyrazino[1,2-a]quinoline)) (**4i**).* A solution of 5 mmol (0.71 g) of acid **1a** in 50% ethanol (10 ml) was added to a solution of 5 mmol (1.24 g) aldehyde **2i** in hot 90% ethanol (20 ml). The reaction mixture was heated to reflux for 6 h, then water (10 ml) was added, and the solution was allowed to stand at 20 °C overnight. A precipitate was filtered out, washed with 50% ethanol, and dried in air to give a mixture of (*S**,*S**)- and (*S**,*R**)-diastereomers **4i** as yellow crystals, mp 289–291 °C; δ_H (500 MHz, DMSO-d_6) 11.69 and 11.53 (0.46H+0.54H, s+s, N*H*, *S**,*R** and *S**,*S**), 7.92 (1H, m, H_{arom}), 7.79 (1H, d, *J* 2.4 Hz, H_{arom}), 6.97 (1H, m, H_{arom}), 4.15 (1H, m, NC*H*), 3.71 and 3.34 (2H, m, NCH_aH_b), 3.26 and 3.09 (1H+1H, d+d, *J* 16.5 Hz, CH_aH_bAr), 3.20 and 3.10 (1.38H+1.62H, s+s, N*Me*, *S**,*R** and *S**,*S**), 2.81 and 2.05 (1H+1H, m, NCH_aH_b), 2.64 and 1.77 (1H+1H, m, *J* 9.0 Hz, NCH_aH_b), 2.22 (3H, s, N*Me*).

4.4.2. (S,S*)-1-tert-Butyl-2,4,6-trioxospiro(perhydro-pyrimidino-5,5′-(3′-methyl-8′-nitro-1′,2′,3′,3a′,4′,5′-hexahydro-1H-pyrazino[1,2-a]quinoline)) (**4s**).* Yellow acicular crystals, mp 260 °C (decomp.); [found: C 57.75, H 6.23, N 16.92. $C_{20}H_{25}N_5O_5$ requires C 57.82, H 6.07, N 16.86%]; δ_H (500 MHz, DMSO-d_6) 11.22 (1H, s, N*H*), 7.95 (1H, d, *J* 2.2 Hz, H_{arom}), 7.91 (1H, dd, *J* 9.3, 2.2 Hz, H_{arom}), 6.95 (1H, d, *J* 9.3 Hz, H_{arom}), 4.23 and 3.20 (2H, m, *J* 13.5 Hz, NCH_aH_b), 3.89 (1H, dd, *J* 9.4, 5.0 Hz, NC*H*), 3.35 and 3.05 (1H+1H, d+d, *J* 16.4 Hz, CH_aH_bAr), 2.66 and 1.84 (1H+1H, m, *J* 10.5 Hz, NCH_aH_b), 2.59 and 2.04 (1H+1H, m, NCH_aH_b), 2.20 (3H, s, N*Me*), 1.51 (9H, s, *t-Bu*); δ_C (200 MHz, DMSO-d_6) 172.05, 166.84, 149.57, 148.49, 137.45, 124.67, 123.44, 122.08, 112.63, 59.84, 59.77, 54.34, 52.64, 51.96, 48.28, 45.44, 28.69, 27.57.

4.5. General procedure for synthesis of 5-arylidene barbiturates 3j,t

*4.5.1. 1-Methyl-5-(2-morpholin-4-yl-5-nitrobenzylidene)-pyrimidine-2,4,6-trione (**3j**).* A solution of 5 mmol (0.71 g) acid **1a** in 50% ethanol (20 ml) was added to a hot solution of 5 mmol (1.18 g) aldehyde **2j** in 94% ethanol (50 ml). The reaction mixture was allowed to stand at 20 °C for 5 days. A precipitate was filtered out, washed with 50% ethanol, and dried in air to give 1.50 g (84%) compound **3t** as yellow-orange prismatic crystals, mp 185 °C; [found: C 53.14, H 4.65, N 15.21. $C_{16}H_{16}N_4O_6$ requires C 53.33, H 4.48, N 15.55%]; δ_H ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.73+8.70 (1H, d+d, *J* 2.6 Hz, H_{arom}, *E*+*Z*), 8.25 (1H, dd, *J* 8.4, 2.6 Hz, H_{arom}), 8.23+8.20 (1H, s+s, =C*H*, *E*+*Z*), 7.18 (1H, d, *J* 8.4 Hz, H_{arom}), 3.80 (4H, t, *J* 5.5 Hz, 2 OCH_2), 3.27+3.22 (3H, s+s, N*Me*, *E*+*Z*), 3.18 (4H, t, *J* 5.0 Hz, 2NCH_2).

*4.5.2. 1-tert-Butyl-5-(2-morpholin-4-yl-5-nitrobenzylidene)-pyrimidine-2,4,6-trione (**3t**).* It was prepared from aldehyde **2j** and acid **1k** in 82% yield. Yellow-orange prismatic crystals, mp 160 °C. For ^{1}H NMR, see the above text. Found, %: C 56.63, H 5.60, N 13.86. $C_{19}H_{22}N_4O_6$. Requires C 56.71, H 5.51, N 13.92%].

4.6. General method C—the procedure for synthesis of 5-spiro barbiturates 4j,t (Table 1)

*4.6.1. 1-Methyl-2,4,6-trioxospiro(perhydropyrimidino-5,5′-(8′-nitro-1′,3′,4′,9′,10′,10a′-hexahydro-2-oxa-4a-phenanthrene)) (**4j**).* A solution of 5 mmol (0.71 g) acid **1a** in 20 ml 50% ethanol were added to a solution of 2 mmol (0.72 g) compound **3t** in 40 ml 94% ethanol containing 0.5 ml of dimethylacetamide. The reaction mixture was refluxed for 6 h, cooled down, after which 40 ml water was added. A precipitate was filtered out, washed with 50% ethanol and dried in air to give compound **4j** as a mixture of (*S**,*S**)- and (*S**,*R**)-diastereomers, pale-yellow acicular crystals, mp 301–303 °C; [found: C 53.20, H 4.57, N 15.36. $C_{16}H_{16}N_4O_5$ requires C 53.33, H 4.48, N 15.56%]; δ_H (500 MHz, DMSO-d_6) 11.74 and 11.55 (0.5H+0.5H, s+s, N*H* (*S**,*S** and *S**,*R**)), 7.95 (1H, dd, *J* 9.5, 2.4 Hz, H_{arom}), 7.82 (1H, d, *J* 2.4 Hz, H_{arom}), 6.95 (1H, d, *J* 9.5 Hz, H_{arom}), 4.07+3.75+3.56 (1H+2H+1H, m+m+m, OCH_aH_b+NCH_aH_b), 3.93 (1H, m, NC*H*), 3.35–3.18 (4H, m, CH_2Ar+OCH_2), 3.20 and 3.10 (1.5H+1.5H, s+s, N*Me*, *S**,*S** and *S**,*R**).

*4.6.2. 1-tert-Butyl-2,4,6-trioxospiro(perhydropyrimidino-5,5′-(8′-nitro-1′,3′,4′,9′,10′,10a′-hexahydro-2-oxa-4a-phenanthrene)) (**4t**).* Mixture of (*S**,*S**)- and (*S**,*R**)-diastereomers, mp 245–248 °C (decomp.); δ_H (500 MHz, DMSO-d_6) 11.39 and 11.20 (0.3H+0.7H, s+s, NH, *S**,*R** and *S**,*S**), 7.90 (2H, m, H_{arom}), 6.93 (1H, d, *J* 9.0 Hz, H_{arom}), 4.10+3.78+3.52+3.35 (2H+1H+2H+1H, m+m+m+m, 2OCH_aH_b+NCH_aH_b), 3.98 (1H, m, NC*H*), 3.31 and 3.05 (1H+1H, d+d, *J* 16.7 Hz, CH_aH_bAr), 1.55 and 1.49 (6.3H+2.7H, s+s, *t-Bu*, *S**,*S**, and *S**,*R**).

Recrystallzation from ethanol gave the pure (*S**,*S**)-diastereomer **4t** as pale-yellow acicular crystals, mp 248 °C (decomp.); [found: C 56.60, H 5.50, N 13.88. $C_{19}H_{22}N_4O_6$ requires C 56.71, H 5.51, N 13.92%]; δ_C (200 MHz, DMSO-d_6); 170.54, 167.69, 149.88, 136.45, 124.03, 124.22, 121.36, 111.14, 66.65, 66.23, 57.71, 54.47, 48.84, 46.15, 28.72, 27.66.

4.7. Method D—the procedure for synthesis of (*S**,*S**)-1-methyl-2,4,6-trioxospiro(perhydropyrimidino-5,5′-(8′-nitro-1′,3′,4′,9′,10′,10a′-hexahydro-2-oxa-4*a*-phenanthrene)) (4j) (Table 1) in the solid phase

Crystals **3t** (2 mmol (0.72 g)) were kept in a sealed ampoule at 120 °C for 72 h to obtain a mixture of (*S**,*S**)- and (*S**,*R**)-diastereomers **4j** (see Table 1). This mixture was boiled in 50% ethanol (50 ml) for 10 min and then hot-filtered. A precipitate was recrystallized from glacial acetic acid and vacuum-dried over KOH to give 0.21 g (29%) the (*S**,*S**)-diastereomer of **4j** as pale-yellow acicular crystals, mp 305–307 °C (decomp.); [found: C 53.25, H 4.53, N 15.50. $C_{16}H_{16}N_4O_6$ requires C 53.33, H 4.48, N 15.56%]; δ_H (500 MHz, DMSO-d_6) 11.55 (1H, s, N*H*), 7.95 (1H, dd, *J* 8.5, 2.2 Hz, H_{arom}), 7.82 (1H, d, *J* 2.2 Hz, H_{arom}), 6.95 (1H, d, *J* 8.5 Hz, H_{arom}), 4.07+3.80+3.77+3.56 (1H+1H+1H+1H, m+m+m+m, OCH_aH_b+NCH_aH_b), 3.93 (1H, dd, *J* 9.5, 4.6 Hz, NC*H*), 3.35–3.23 (4H, m, CH_2Ar+OCH_2), 3.20 (3H, s, N*Me*); δ_C (200 MHz, DMSO-d_6) 170.15, 167.44, 149.99, 136.92, 124.20, 123.71, 120.78, 111.25, 66.68, 66.04, 58.14, 48.64, 46.38, 34.41, 28.10.

Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.06.015.

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