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New findings in the alkylation and N-deprotection of (4*S*)-4-methyl-2-benzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones

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Abstract

Alkyl halides behave differently to benzyl halides in C-1 alkylation of the title compounds. The *syn* and *anti* 1,4-disubstituted diastereomers thus obtained show different regioselectivity by further alkylation leading to the 1,4,4- and 1,1,4-trisubstituted compounds, respectively. Alkylation is always directed *anti* with respect to the bulkier substituent at C-1 or C-4. Debenzylation attempts on 2-benzyl-derivatives **1b** by treatment with HCOOH and C/Pd or H_2/C–Pd/MeOH/H^+ led to C-1 oxidised or 7,8,9,10-tetrahydro-derivatives. Deprotection of 2-*p*-methoxybenzyl- and 2-(2,4-dimethoxybenzyl)-derivatives with CAN and with TFA/anisole, respectively, was successful, but in the latter case epimerization at C-1 occurred.

The 2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione system **C**, is a fragment of the fungal metabolite *N*-acetylardeemin **A**, (Fig. 1) which has been described as a potent reversal agent of multiple drug resistance (MDR) in tumour cell lines.[1] A variety of fungal metabolites, such as glyantrypine,[2a] fumiquinazolines F and G[2b,c] or fiscalin B,[2d] are also derivatives of **C**, and a convergent synthetic route to *N*-acetylardeemin analogues features the cyclization of compounds **B** (R^1=3-indolylmethyl), which can be prepared by alkylation of N-protected derivatives **C** (R^1=H) as the key step.[3a]

N-Protection of **B** is required in its synthesis by condensation of piperazinedione bislactim ethers and anthranilic acid, in order to avoid formation of compounds such as **2** in the synthesis of C-1 unsubstituted **1a** (Scheme 1). Furthermore, *N*-arylmethyl groups allow an easy manipulation of the starting piperazine-2,5-diones, because of their increased lipophilicity, being at the same time relatively stable towards electrophilic substitution conditions.

We have recently reported[3a] that compounds **1b**,**c** (Scheme 2) are regioselectively alkylated in base at C-1 and that the asymmetric induction of the C-4 stereocentre directs the attack of benzyl halides to

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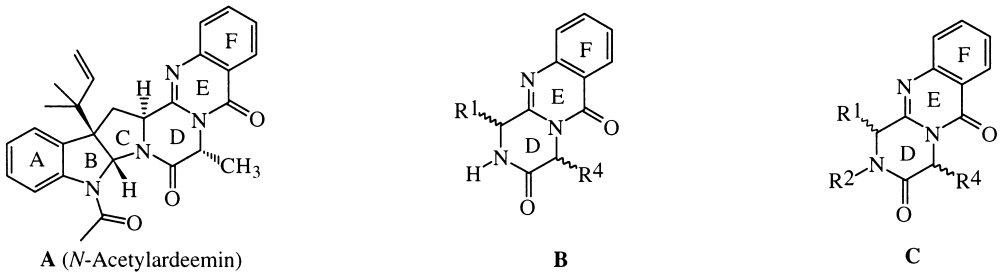
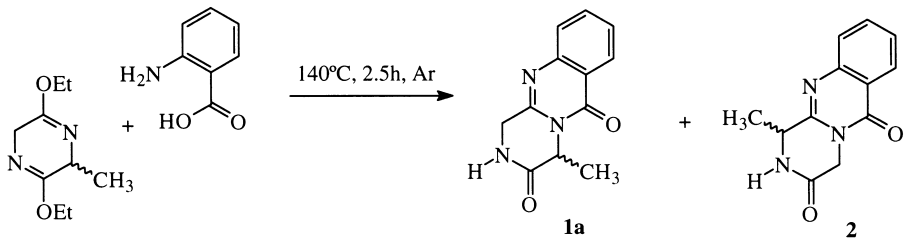
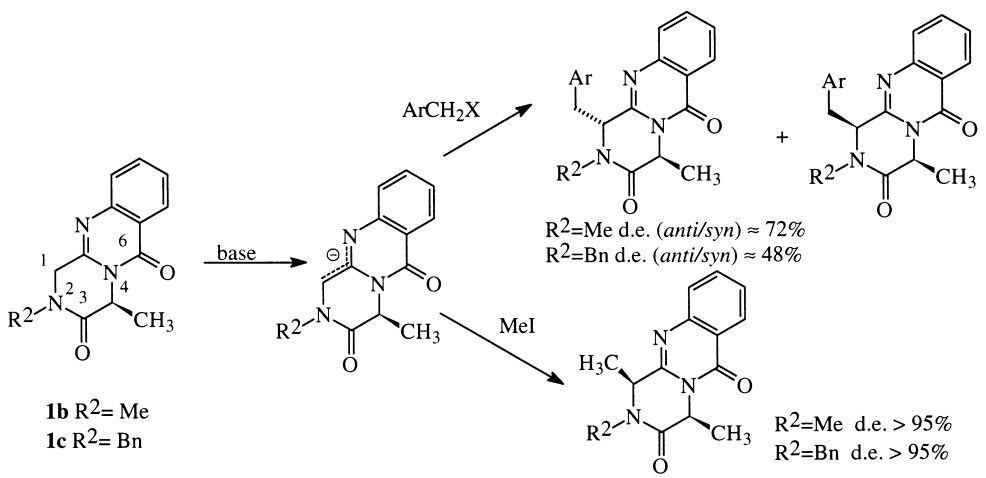


Fig. 1.



Scheme 1.

give (1*R*,4*S*)-diastereomers with an *anti*-configuration for the alkyl groups at C-1 and C-4. Due to 1,2-interactions of the pseudoequatorial C-1 and *N*-2 substituents, the (1*R*,4*S*) *anti*-isomers equilibrate to the (1*S*,4*S*) *syn*-isomers, which are the thermodynamic products, by deprotonation at C-1. The diastereomeric excess is dependant on the volume of the R^2 substituent, being lower for **1c** derivatives.



Scheme 2.

The *syn*- and *anti*-isomers can clearly be distinguished by NOE experiments. Irradiating the C^4–CH_3 (Fig. 2), NOE is registered on C^1–H and R^1–H in *anti*- and *syn*-isomers, respectively, which suggests a boat conformation for both isomers, with the C^4-methyl group in axial or pseudoaxial disposition. Different δ values for the C-4 proton in the ^{1}H NMR are observed, around 5.3 ppm in the *syn*-isomers and around 4 ppm in the *anti*-isomers. This difference shows that the pyperazine ring adopts a boat conformation in the *syn*-isomers with the C-1 and C-4 substituents in a pseudoaxial disposition, the C-4 proton being strongly deshielded by the C-6 carbonyl group, while this ring is more planar in the *anti*-isomers, because of the previously mentioned 1,2 steric interactions (Fig. 2).[3,4]

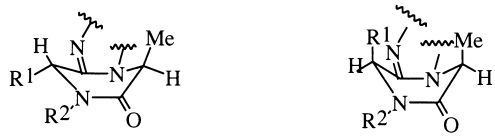
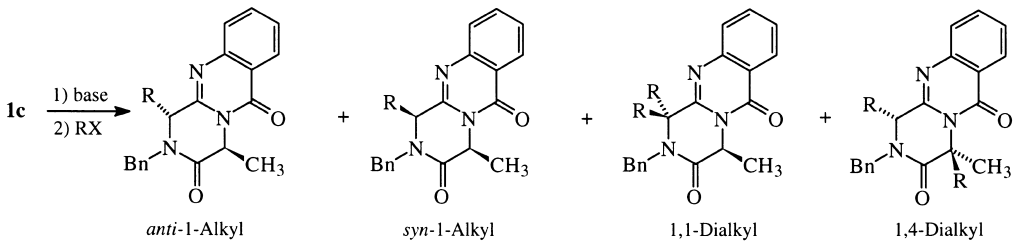


Fig. 2. Conformation of the piperazine ring in 1,4-dialkyl *anti*- and *syn*-isomers

Table 1



Entry	R[a]	*anti*-1-Alkyl[a]	*syn*-1-Alkyl[a]	1,1-Dialkyl[a]	1,4-Dialkyl[a]
1	allyl[c]	35[3a]	21[3a]	28 (**16c**)	---
2	*p*-Me-C_6H_4-CH_2	24[3a] (**9c**)	31[b] (**9c**)	7[b] (**17c**)	12[b] (**13c**)
3	Bn[d]	---	---	77 (**18c**)	---

[a] Yield (%); [b] racemic; [c] reaction time 1h; [d] 1) 2 LHMDS, DMEU; 2) 2 eq BnBr, 0.5h

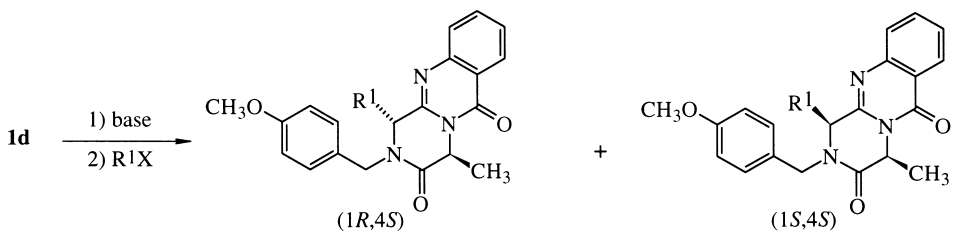
The exclusive isolation of the *syn*-isomers in the alkylation with methyl iodide (Scheme 2) was supposed to be due to a slower S_N2 mechanism, compared to the S_N1 reactions that occur with most benzyl halides,[5] and to a faster equilibration of 1-methyl *anti*-isomers with respect to the 1-benzyl derivatives due to steric effects.[6] Different experiments also suggested that the formation of racemic (1*S**, 4*S**)-compounds during long reaction times was due to deprotonation at C-4 and C-1.[3a] Thus, benzylation of **1c** with an excess of alkylating agent during prolonged reaction times (12 h) gave lower yields of the *anti*-isomers in favour of the *syn*-isomers, which racemized (Table 1, entries 1 and 2). From this reaction mixture 1,1- and 1,4-dialkylated derivatives were also isolated. On the other hand, treatment of **1c** with 2 equivalents of base, benzyl bromide and DMEU as cosolvent gave exclusively the 1,1-dibenzyl derivative **18c** in good yields (Table 1, entry 3).

Since 1,1- and 1,4-dialkyl compounds derive from further alkylation of the initially formed *anti*- or *syn*-1-alkyl-diastereoisomers, it can be supposed that the regioselectivity of the second reaction depends on the *anti* or *syn* stereochemistry of the initially formed substrates. To confirm these assumptions and to extend the understanding of this reaction, we first studied the alkylation of **1d** (R^2=*p*-$MeOC_6H_4$–CH_2). It can be seen in Table 2 that methyl and benzyl halides behaved as expected giving *syn*-**3d** and *anti*-**7d** as exclusive or major products, respectively. Ethyl bromoacetate and *n*-butyl iodide, for which an S_N2 mechanism was supposed, gave the *syn*-isomers **4d** and **5d** in great d.e., while isopropyl iodide gave racemic **6d**.[7] These results confirm that S_N2 reactions give the thermodynamic products and that racemization implies C-4 anions.

Again, *syn*- and *anti*- isomers mainly differ in their δ H-4 values (Δδ=1.3 ppm for **4d** and **7d**). In the case of **5d** the chemical shift of H-4 is similar in both isomers suggesting a similar boat conformation. Traces of (1*R*,4*S*)-1-hydroxy derivative **19d** were also obtained, showing the sensitivity of this system to be oxidised at C-1 (see later).

The regioselectivity of the second alkylation step was studied next. Enantiopure *syn*-**3d** was treated

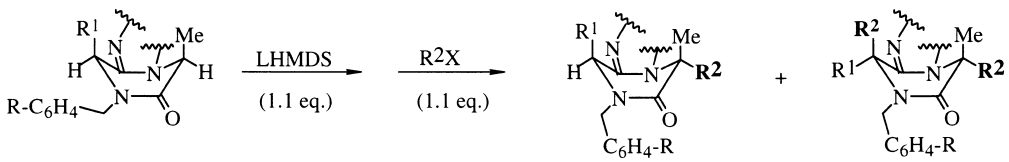
Table 2



Compound	R^1X	Yield	*anti/syn*	d.e. (%)
3d	MeI	60[a]	0/100	>95
4d	$EtOOCCH_2Br$	71	10/90	80
5d	*n*-BuI	87[b]	9/91	82
6d	*i*-PrI	71	0/100[c]	>95
7d	BnBr	78	77/23	54

[a] 33% yield of (1*S*)-1,4,4-trimethyl-2-(4-methoxybenzyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (**11d**) was also isolated. [b] Traces of (1*R*,4*S*)-1-hydroxy derivative **19d** (R^1= OH, *anti*-isomer) were also formed.
[c] (1*S**,4*S**).

with LHMDS and either methyl iodide or *p*-methylbenzyl bromide. The stereochemistry of the 1,4,4-trialkyl derivatives thus obtained (compounds **11d** and **12d**, Scheme 3) showed that the diastereoselection is imposed by the C-1 centre. The stereochemistry of the 1,1,4,4-tetra-alkyl compound **20d** also showed that additional alkylation of **12d** is controlled by the bulkier substituent at C-4. An additional reactivity confirmation for the *syn*-1,4-disubstituted derivatives was obtained when *syn*-**9c** was alkylated with *p*-methylbenzyl bromide and **13c** was produced. The configuration of all compounds was determined by NOE experiments (see Experimental and Fig. 3).



syn-**3d** R = *p*-CH_3O, R^1= CH_3
syn-**9c** R = H, R^1= *p*-$MeC_6H_4CH_2$

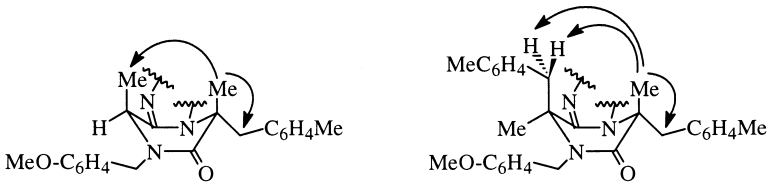
11, **12**, **13** **20**

11d	R=OCH_3, R^1=R^2=CH_3	33%
12d	R=OCH_3, R^1=CH_3, R^2= *p*-Me-$C_6H_4CH_2$	56%
20d	R=OCH_3, R^1=CH_3, R^2= *p*-Me-$C_6H_4CH_2$	18%
13c	R=H, R^1=R^2=*p*-Me-$C_6H_4CH_2$	22%

Scheme 3.

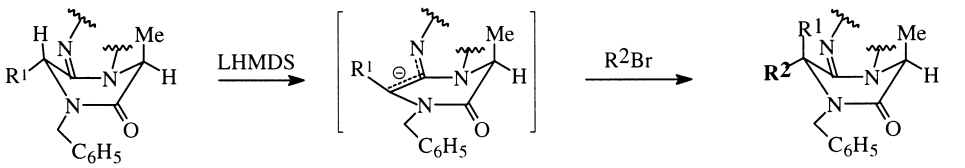
On the other hand, when the *anti*-isomers **9c** and **10c** (Scheme 4) were treated with LHMDS and *p*-fluorobenzyl or *p*-methylbenzyl bromide, respectively, we got, instead of the 1,4-dialkyl derivatives, the 1,1-dialkylated compounds **14c** and **15c**, respectively.

In conclusion, *syn*-1,4-dialkyl-2-benzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones are regioselectively alkylated at C-4 while the *anti*-isomers are alkylated at C-1. This behaviour differs from that of the 2-methyl analogues where both, *anti*- and *syn*- 1,4-dialkyl isomers are regioselectively



12d **20d**

Fig. 3. NOEs registered on **12d** and **20d**



anti-**9c** R1 = *p*-Me-$C_6H_4CH_2$

anti-**10c** R1 = *p*-F-$C_6H_4CH_2$

14c R1 = *p*-Me-$C_6H_4CH_2$, R2 = *p*-F-$C_6H_4CH_2$ 41%

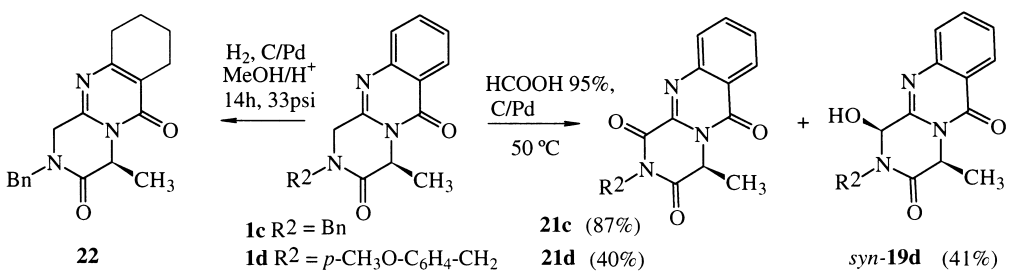
15c R1 = *p*-F-$C_6H_4CH_2$, R2 = *p*-Me-$C_6H_4CH_2$ 53%

Scheme 4.

alkylated at C-1.[3b] The greater 1,2-steric interaction at the planar C-1 anion in compounds **c** and **d** (where R^2=benzyl) than in compounds **b** (where R^2=methyl) explains the different regioselectivity of *syn*-isomers in 2-methyl and 2-benzyl series.

The difficulty that N-debenzylation of amides presents in some cases is well known.[8] Steglich et al.[9] have studied in particular the debenzylation of peptidic benzylamides in different media, but deprotection of model compounds **1c–e** presented some interesting problems. Attempts of reductive debenzylation of **1c** or **1d** by treatment with 95% formic acid under argon atmosphere at rt or 50°C[10] were unsuccessful being starting compounds recovered. The same result was obtained in the treatment of **1c** with formic acid and C/Pd at rt.[11] When this reaction was performed at 50°C, oxidation compounds **21c**, **21d** and *syn*-**19d** were obtained.

Furthermore catalytic hydrogenation of **1c** was unsuccessful with recovery of the starting material, while hydrogenation in acidic medium (methanol/formic acid 5%) at rt and 33 psi produced partial hydrogenation of the fused benzene ring, giving compound **22** (Scheme 5) instead of the desired reductive debenzylation. Finally, the reductive debenzylation of **1c** with sodium and liquid ammonia in THF led to decomposition.



22

1c R^2 = Bn

1d R^2 = *p*-CH_3O-C_6H_4-CH_2

21c (87%)

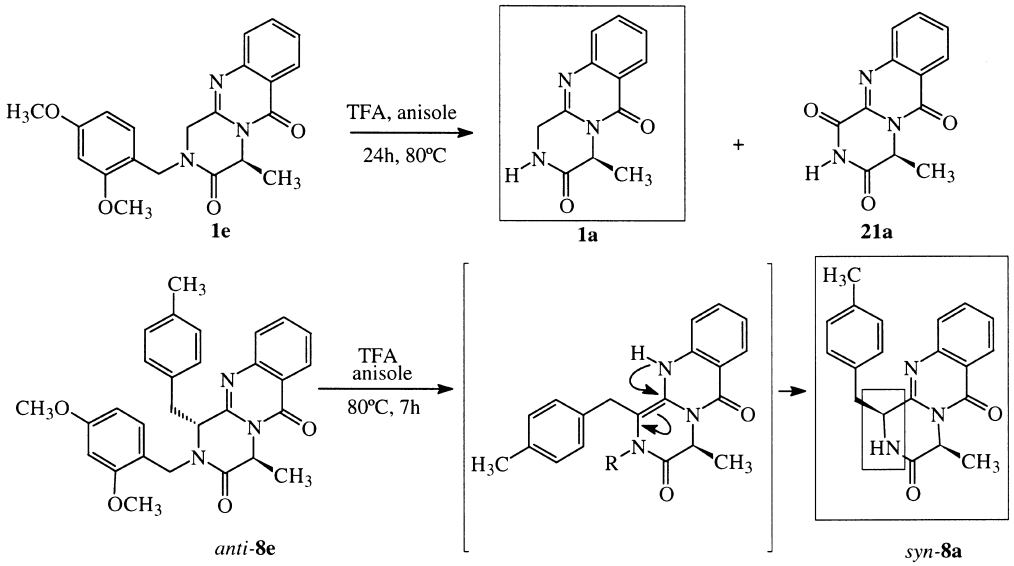
21d (40%)

syn-**19d** (41%)

Scheme 5.

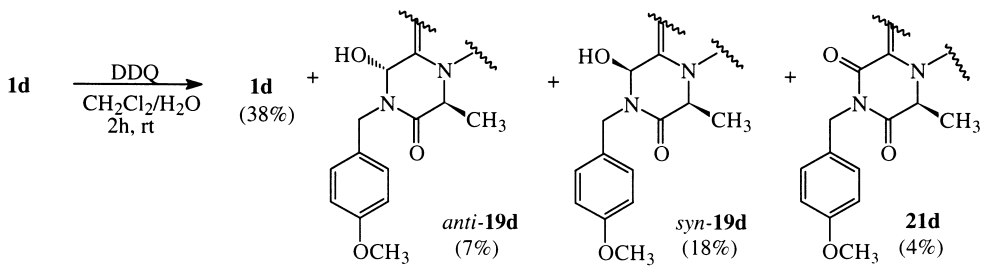
Debenzylation with strong organic acids, which requires benzyl groups carrying electron donor substituents, was investigated with **1e**. After several experiments we found that treatment of **1e** with

trifluoroacetic acid and anisole as a cation captor[12] gave **1a** in 68% yield together with traces of **21a** (Scheme 6). This procedure was successful when applied to the 1-alkyl compound *anti*-**8e** but, unfortunately, epimerization of the C-1 stereocentre also took place,[13] giving *syn*-**8a** quantitatively. Similar isomerizations at C-1 in acid media have also been observed for fumiquinazolines.[14,15]



Scheme 6.

These results forced us to apply the oxidative debenzylation on **1d** and **1e** by using CAN[8b,16,17] and DDQ.[18] Reaction of **1d** with DDQ (Scheme 7) gave starting compound (38%) together with the *syn*- and *anti*-1-hydroxy-derivatives[13] **19d** (18% and 7%, respectively) and traces of ketone **21d**.

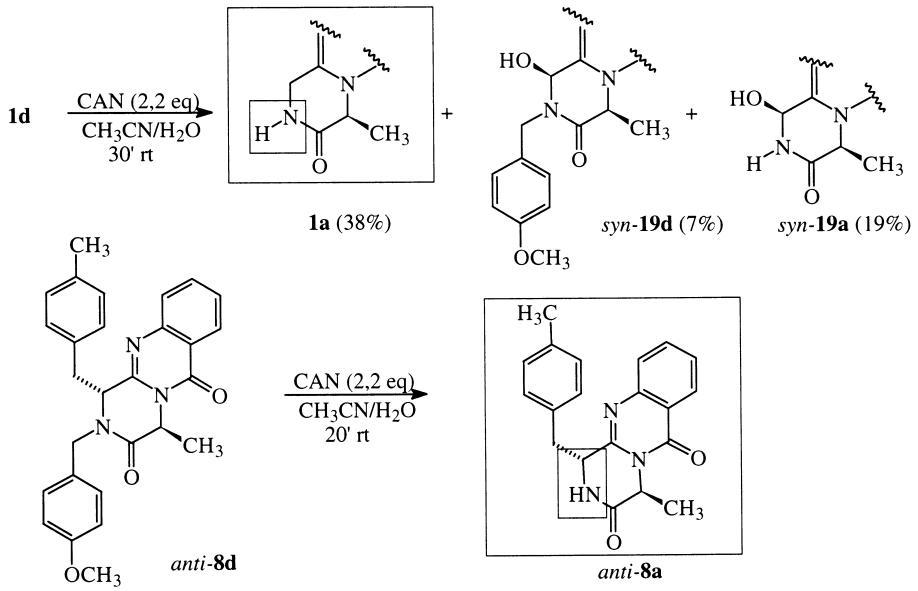


Scheme 7.

The treatment of **1d** with CAN (Scheme 8) allowed the oxidative debenzylation to the desired product **1a** (38%) together with 19% of debenzylated hydroxy derivative *syn*-**19a** and 7% of *syn*-**19d**. Finally, the application of this oxidative debenzylation to the 1-alkyl derivative **8d** led to the debenzylated product *anti*-**8a**, with retention of the configuration, in acceptable yields (72% over recovered starting material).[13]

1. Experimental

Melting points are uncorrected. IR spectra were recorded with all solid compounds compressed into KBr pellets and liquid compounds placed between NaCl plates. NMR spectra were recorded at 250 MHz for ^{1}H and 62.5 MHz for ^{13}C in $CDCl_3$, with TMS as the internal reference (Servicio RMN,



Scheme 8.

U. C. M.). Mass spectra were recorded at 70 eV, quadrupole detector, EI (Centro de Espectroscopía U. C. M.). Elemental analyses were obtained from the Centro de Microanálisis, U. C. M. Optical rotations were determined at 25°C in $CHCl_3$ or EtOH at 589 nm. Separations by chromatography were performed on silica gel (35–70 μm). Tetrahydrofuran was freshly distilled from sodium-benzophenone. All commercial reagents were used as received. The expression 'petroleum ether' refers to the fraction boiling at 40–60°C.

*1.1. (4S)-2-(2,4-Dimethoxybenzyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione* ***1e***

To a stirred solution of 3.6 g (14.2 mmol) of distilled ethyl *N*-(2,4-dimethoxybenzyl)glycinate[19] in 40 ml dry CH_2Cl_2, 3.17 (14.2 mmol) of *N*-Cbz-L-alanine and 3.22 g (15.7 mmol) of DCC were added and stirring was continued overnight. The reaction mixture was filtered, washed successively with HCl (1 N), $NaHCO_3$ (1 N) and water, dried over anhydrous Na_2SO_4 and evaporated. The syrupy residue (6 g, 1.31 mmol; yield 92%) was hydrogenated at 35 psi during 14 h with 0.55 g of C/Pd (10%) in 100 ml methanol, filtered (Celite) and evaporated. The obtained syrup was refluxed in 30 ml of methanol for 12 h, concentrated and recrystallized to give (3*S*)-3-methyl-1-(2,4-dimethoxybenzyl)piperazine-2,5-dione (3.83 g, 78%). Mp: 115–117°C (toluene). $[\alpha]_D$: +5.6 (0.30, $CHCl_3$). IR (KBr) ν: 1690, 1654 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.20 (1H, d, *J*=8.3 Hz, H-6′), 7.19 (1H, s, NH), 6.45 (1H, dd, *J*=8.3, 2.4 Hz, H-5′), 6.43 (1H, d, *J*=2.4 Hz, H-3′), 4.55 (1H, d, *J*=14.3 Hz, Ar–CH_2–N), 4.48 (1H, d, *J*=14.3 Hz, Ar–CH_2–N), 4.05 (1H, q, *J*=7 Hz, H-3), 3.88 (2H, s, H-6), 3.78 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 1.46 (3H, d, *J*=7 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 166.9, 166.7, 161.0, 158.8, 131.8, 116.0, 104.6, 98.5, 55.5, 51.1, 49.4, 44.1, 20.1. Analysis calc. for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.54; H, 6.42; N, 10.12.

A mixture of 5.25 g (18.9 mmol) of the above described (3*S*)-3-methyl-1-(2,4-dimethoxybenzyl)-piperazine-2,5-dione, triethyloxonium tetrafluoroborate (15 g, 79 mmol) and anhydrous Na_2CO_3 (11.1 g, 105 mmol) in 100 ml of dry CH_2Cl_2 was stirred overnight at rt, poured on ice water, extracted with CH_2Cl_2, dried (Na_2SO_4) and evaporated. Anthranilic acid (3.85 g, 28.1 mmol) was added to the syrupy

residue, the mixture was stirred vigorously at 130–140°C for 2.5 h under argon, dissolved in CH_2Cl_2, extracted with diluted ammonium hydroxide, dried (Na_2SO_4) and concentrated. Column chromatography (EtOAc:MeOH 95:5) afforded 3.87 g (54%) of **1e** as a white solid. Mp: 72–73°C (ethyl acetate:methanol). $[\alpha]_D$: +24.7 (0.29, $CHCl_3$). IR (KBr) ν: 1710, 1678 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.26 (1H, ddd, *J*=7.9, 1.5, 0.5 Hz, H-7), 7.73 (1H, ddd, *J*=8.2, 7.1, 1.5 Hz, H-9), 7.58 (1H, ddd, *J*=8.2, 1.2, 0.5 Hz, H-10), 7.46 (1H, ddd, *J*=7.9, 7.1, 1.2 Hz, H-8), 7.23 (1H, d, *J*=9 Hz, H-6′), 6.45 (1H, dd, *J*=9, 2.2 Hz, H-5′), 6.45 (1H, d, *J*=2.2 Hz, H-3′), 5.47 (1H, q, *J*=7.2 Hz, H-4), 4.85 (1H, d, *J*=14.2 Hz, Ar–CH_2–N), 4.49 (1H, *J*=14.2 Hz, Ar–CH_2–N), 4.50 (1H, d, *J*=17.2 Hz, H-1), 4.41 (1H, d, *J*=17.2 Hz, H-1), 3.81 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 1.56 (3H, d, *J*=7.2 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 167.1, 160.9, 159.9, 158.7, 148.5, 147.2, 134.6, 131.7, 127.0, 126.8, 126,7, 120.4, 115.6, 104.4, 98.4, 55.3, 55.3, 52.1, 49.3, 44.4, 16.8. Analysis calc. for $C_{21}H_{21}N_3O_4$: C, 66.48; H, 5.58; N, 11.07. Found: C, 66.03; H, 5.64; N, 10.74.

*1.2. (±)-4-Methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione **1a** and (±)-1-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione **2***

A mixture of 1 g (7.4 mmol) of (±)-3-methylpiperazine-2,5-dione, triethyloxonium tetrafluoroborate (4 g, 22 mmol) and anhydrous Na_2CO_3 (3.9 g, 37 mmol) in 100 ml dry CH_2Cl_2 was stirred for 3 days at room temperature, poured on ice water, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4 and evaporated. Anthranilic acid (1.2 g, 8.7 mmol) was added to the syrupy residue, the mixture was stirred vigorously at 130°C for 2.5 h under argon, dissolved in $CHCl_3$, extracted with diluted ammonium hydroxide, dried (Na_2SO_4) and concentrated. Column chromatography (EtOAc:MeOH 95:5) afforded 160 mg (9%) of (±)-**1a** and 250 mg (14%) of (±)-**2**.

*1.2.1. Data for (±)-**1a***

Mp: 216–218°C ($CHCl_3$:methanol:hexane). Spectral data identical to (+)-**1a** (see later). Analysis calc. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.98; H, 4.70; N, 18.46.

*1.2.2. Data for (±)-**2***

Mp: 240–243°C ($CHCl_3$:methanol:hexane). IR (KBr) ν: 1684 cm^{-1}. ^1H NMR ($CDCl_3$:MeOD) δ: 7.95 (1H, ddd, *J*=7.9, 1.5, 0.6 Hz, H-7), 7.55 (1H, ddd, *J*=8.2, 7.1, 1.5 Hz, H-9), 7.40 (1H, ddd, *J*=8.2, 1.2, 0.6 Hz, H-10), 7.25 (1H, ddd, *J*=7.9, 7.1, 1.2 Hz, H-8), 4.52 (1H, d, *J*=18 Hz, H-4), 4.40 (1H, q, *J*=7 Hz, H-1), 4.35 (1H, d, *J*=18.0 Hz, H-4), 1.45 (3H, d, *J*=7.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$:MeOD) δ: 166.5 (C-3), 160.8 (C-6), 151.8 (C-11a), 146.9 (C-10a), 134.8 (C-9), 127.2, 126.8 and 126.4 (C-7, 8 and 10), 119.6 (C-6a), 51.1 (C-4), 44.2 (C-1), 19.8 (CH_3). Analysis calc. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 63.09; H, 4.63; N, 18.57.

1.3. General alkylation procedures

Method A: To a cold (−78°C), magnetically stirred solution of 1 mmol of **1d**[20] (if not otherwise indicated) in dry THF (15 ml) was added, under argon, drop wise via syringe a 1 M solution of lithium hexamethyldisilazide in THF (1 ml), followed by the adequate halide (1.1 mmol dissolved in 5 ml of THF) 10 min later. The reaction mixture was maintained at −78°C for 10 min and at 0°C for 30 min (if not indicated otherwise) quenched with a cold saturated ammonium chloride solution and diluted with CH_2Cl_2. The separated aqueous layer was extracted with CH_2Cl_2 (3×20 ml) and the combined organic layers were washed with water, dried and evaporated. Chromatography of the residue on silica

gel provided first the 1,4-dialkylated and 1,1-dialkylated, if any, followed by the *anti*-1-alkylated and *syn*-1-alkylated compounds.

Method B: To a cold (−78°C), magnetically stirred solution the corresponding 2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (0.5 mmol) and 1,3-dimethylimidazolidin-2-one (DMEU) (0.5 mmol) in dry THF (15 ml) was added, under argon, drop wise via syringe a 1 M solution of lithium hexamethyldisilazide in THF (0.6 ml), followed by the adequate halide (0.6 mmol dissolved in 5 ml of THF) 10 min later. The reaction mixture was maintained at −78°C for 10 min and at 0°C for 30 min and worked up as indicated for Method A.

Method C: To a cold (−78°C), magnetically stirred solution of **1c**[3a] (0.5 mmol) and 1,3-dimethylimidazolidin-2-one (DMEU) (1 mmol) in dry THF (15 ml) was added, under argon, drop wise via syringe a 1 M solution of lithium hexamethyldisilazide in THF (1.1 ml), followed by the adequate halide (1.1 mmol dissolved in 5 ml of THF) 10 min later. The reaction mixture was maintained at −78°C for 10 min and at 0°C for 30 min and worked up as indicated for Method A.

*1.4. (1S,4S)-1,4-Dimethyl-2-*p*-methoxybenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (*syn-***3d***) and (1S)-2-*p*-methoxybenzyl-1,4,4-trimethyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione* ***11d***

Method A: Column chromatography (ethyl acetate:petroleum ether 7:3) affords *syn*-**3d** and **11d**.

Method B: Starting from *syn*-**3d**, **11d** was obtained in 33% yield.

1.4.1. Data for syn-***3d***

Mp: 122–124°C (ethyl acetate:petroleum ether). $[\alpha]_D$: +23.0 (0.14, chloroform). IR (KBr) ν: 1684, 1659, 1602 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.21 (1H, dd, *J*=8.0, 1.1 Hz, H-7), 7.69 (1H, ddd, *J*=7.7, 7.1, 1.1 Hz, H-9), 7.51 (1H, dd, *J*=7.7, 1.2, H-10), 7.42 (1H, ddd, *J*=8.0, 7.1, 1.2 Hz, H-8), 7.21 (2H, d, *J*=8.7 Hz, H-2′ and 6′), 6.81 (2H, d, *J*=8.7 Hz, H-3′ and 5′), 5.37 (1H, q, *J*=7.2 Hz, H-4), 5.23 (1H, d, *J*=14.7 Hz, Ar–CH_2–N), 5.11 (1H, q, *J*=7.1 Hz, H-1), 4.07 (1H, d, *J*=14.7 Hz, Ar–CH_2–N), 3.73 (3H, s, OCH_3), 1.72 (3H, d, *J*=7.2 Hz, CH_3 (4)), 1.62 (3H, d, *J*=7.1 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 167.1, 160.4, 159.6, 151.8, 147.4, 134.8, 130.0, 127.6, 127.1, 126.9, 126.8, 120.3, 114.5, 55.5, 55.4, 52.3, 47.1, 21.4, 18.5. Analysis calc. for $C_{21}H_{21}N_3O_3$: C, 69.41; H; 5.82; N, 11.56. Found: C, 69.05; H, 6.05; N, 11.34.

1.4.2. Data for ***11d***

Mp: 61–62°C (ethyl acetate:petroleum ether). $[\alpha]_D$: −1.3 (0.35, dichloromethane). IR (KBr) ν: 1683, 1600 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.20 (1H, dd, *J*=8.0, 1.2 Hz, H-7), 7.68 (1H, ddd, *J*=8.5, 7.6, 1.2 Hz, H-9), 7.48 (1H, dd, *J*=7.6, 1.1 Hz, H-10), 7.41 (1H, ddd, *J*=8.5, 8.0, 1.1 Hz, H-8), 7.20 (2H, d, *J*=8.7 Hz, H-2′ and 6′), 6.84 (2H, d, *J*=8.7 Hz, H-3′ and 5′), 5.31 (1H, d, *J*=14.7 Hz, Ar–CH_2–N), 4.48 (1H, q, *J*=6.7 Hz, H-1), 4.02 (1H, d, *J*=14.7 Hz, Ar–CH_2–N), 3.76 (3H, s, OCH_3), 2.08 (3H, s, CH_3), 2.04 (3H, s, CH_3), 1.53 (3H, d, *J*=6.7 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 170.3, 162.2, 159.6, 151.8, 146.7, 134.6, 129.8, 127.7, 127.0, 126.9, 126.4, 121.8, 114.5, 64.4, 55.4, 55.0, 47.5, 25.3, 24.8, 22.3. Analysis calc. for $C_{22}H_{23}N_3O_3$: C, 70.01; H, 6.14; N, 11.13. Found: C, 69.83; H, 6.12; N, 10.99.

*1.5. (1R,4S)-1-Ethoxycarbonylmethyl-2-*p*-methoxybenzyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (*anti-***4d***) and (1S,4S)-1-ethoxycarbonylmethyl-2-*p*-methoxybenzyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (*syn-***4d***)*

Method A: Column chromatography: ethyl acetate:petroleum ether (7:3).

1.5.1. Data for anti-***4d***

^{1}H NMR ($CDCl_3$) δ: 8.00 (1H, dd, *J*=8.0, 1.2 Hz, H-7), 7.76 (1H, ddd, *J*=7.6, 7.1, 1.2 Hz, H-9), 7.60 (1H, dd, *J*=7.6, 1.2 Hz, H-10), 7.48 (1H, ddd, *J*=8.0, 7.1, 1.2 Hz, H-8), 7.20 (2H, d, *J*=8.7 Hz, H-2′ and 6′), 6.88 (2H, d, *J*=8.7 Hz, H-3′ and 5′), 5.60 (1H, d, *J*=15.5 Hz, Ar–CH_2–N), 4.91 (1H, dd, *J*=6.2, 3.9 Hz, H-1), 4.08 (2H, q, *J*=7.1 Hz, O–*CH_2*–CH_3), 4.00 (1H, q, *J*=6.6 Hz, H-4), 3.88 (1H, d, *J*=15.5 Hz, Ar–CH_2–N), 3.79 (3H, s, OCH_3), 3.27 (1H, dd, *J*=16.6, 3.9 Hz, H-α), 3.18 (1H, dd, *J*=16.6, 6.2 Hz, H-α), 1.40 (3H, d, *J*=6.6 Hz, CH_3), 1.18 (3H, *J*=7.1 Hz, OCH_2–*CH_3*). ^{13}C NMR ($CDCl_3$) δ: 169.9, 167.7, 159.7, 159.0, 145.5, 145.0, 135.6, 128.8, 128.1, 127.7, 126.8, 126.7, 120.2, 114.7, 61.7, 55.3, 54.3, 52.3, 46.4, 41.4, 18.5, 14.3.

1.5.2. Data for syn-***4d***

$[\alpha]_D$: +17.3 (0.45, chloroform). IR (NaCl) ν: 1732, 1684, 1610 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 8.21 (1H, dd, *J*=8.0, 1.1 Hz, H-7), 7.68 (1H, ddd, *J*=7.6, 7.1, 1.1 Hz, H-9), 7.51 (1H, dd, *J*=7.6, 1.2 Hz, H-10), 7.42 (1H, ddd, *J*=8.0, 7.1, 1.2 Hz, H-8), 7.24 (2H, d, *J*=8.7 Hz, H-2′ and 6′), 6.82 (2H, d, *J*=8.7 Hz, H-3′ and 5′), 5.37 (1H, q, *J*=7.2 Hz, H-4), 5.19 (1H, d, *J*=14.6 Hz, Ar–CH_2–N), 5.02 (1H, ′t′, *J*=6.4 Hz, H-1), 4.33 (1H, d, *J*=14.6 Hz, Ar–CH_2–N), 4.07 (2H, q, *J*=7.1 Hz, O–*CH_2*–CH_3), 3.73 (3H, s, OCH_3), 2.86 (1H, dd, *J*=15.2, 6.6 Hz, H-α), 2.93 (1H, dd, *J*=15.2, 6.6 Hz, H-α), 1.73 (3H, d, *J*=7.2 Hz, CH_3), 1.20 (3H, *J*=7.1 Hz, OCH_2–*CH_3*). NOE (δ; %): irradiate Me (1.73), observe H-α (2.93; 2.1) and H-4 (5.37; 8.9). ^{13}C NMR ($CDCl_3$) δ: 169.4, 167.2, 160.3, 159.6, 149.9, 147.2, 134.8, 130.1, 127.5, 127.3, 127.2, 126.8, 120.4, 114.4, 61.7, 56.7, 55.3, 52.2, 47.5, 41.4, 19.1, 14.2. Analysis calc. for $C_{24}H_{25}N_3O_5$: C, 69.19; H, 5.79; N, 9.65. Found: C, 69.35; H, 5.71; N, 9.57.

*1.6. (1*R,*4*S*)-1-n-Butyl-2-*p*-methoxybenzyl-4-methyl-2,4-dihydro-1*H*-pyrazino-[2,1-*b*]quinazoline-3,6-dione (*anti-***5d***), (1*S,*4*S*)-1-n-butyl-2-*p*-methoxybenzyl-4-methyl-2,4-dihydro-1*H*-pyrazino-[2,1-*b*]quinazoline-3,6-dione (*syn-***5d***) and (1*R,*4*S*)-1-hydroxy-4-methyl-2-*p*-methoxybenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione* anti-***19d***

Method A: Reaction time: 2 h at −78°C and 4 h at 0°C; column chromatography (ethyl acetate:petroleum ether 6:4).

1.6.1. Data for anti-***5d***

Mp: 129–131°C (ethyl ether). $[\alpha]_D$: +50 (0.18, chloroform). IR (KBr) ν: 1682, 1610 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 8.24 (1H, dd, *J*=8.0, 1.2 Hz, H-7), 7.73 (1H, ddd, *J*=8.1, 7.9, 1.2 Hz, H-9), 7.57 (1H, dd, *J*=7.9, 1.1 Hz, H-10), 7.45 (1H, ddd, *J*=8.1, 8.0, 1.1 Hz, H-8), 7.21 (2H, d, *J*=8.6 Hz, H-2′ and 6′), 6.87 (2H, d, *J*=8.6 Hz, H-3′ and 5′), 5.64 (1H, d, *J*=14.8 Hz, Ar–CH_2–N), 5.36 (1H, q, *J*=6.7 Hz, H-4), 4.53 (1H, dd, *J*=4.7, 1.9 Hz, H-1), 3.86 (1H, d, *J*=14.8 Hz, Ar–CH_2–N), 3.78 (3H, s, OCH_3), 2.31–2.12 (2H, m, H-α), 1.67 (3H, d, *J*=6.7 Hz, CH_3), 1.22 (4H, m, H-β and γ), 1.22 (3H, m, H-δ). ^{13}C NMR ($CDCl_3$) δ: 168.0, 160.5, 159.5, 150.3, 147.2, 134.8, 129.5, 127.6, 127.1, 127.0, 126.9, 120.4, 114.5, 57.1, 55.4, 52.0, 45.3, 31.8, 24.8, 22.6, 20.4, 14.0. Analysis calc. for $C_{24}H_{27}N_3O_3$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.86; H, 6.71; N, 10.22.

1.6.2. Data for syn-***5d***

Mp: 109–110°C (ethyl ether). $[\alpha]_D$: +3.4 (0.30, chloroform). IR (KBr) ν: 1668, 1603 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 8.26 (1H, dd, *J*=8.0, 1.3 Hz, H-7), 7.72 (1H, ddd, *J*=7.6, 7.2, 1.3 Hz, H-9), 7.57 (1H, dd, *J*=7.6, 1.2 Hz, H-10), 7.45 (1H, ddd, *J*=8.0, 7.2, 1.2 Hz, H-8), 7.18 (2H, d, *J*=8.7 Hz, H-2′ and 6′), 6.83 (2H, d, *J*=8.7 Hz, H-3′ and 5′), 5.37 (1H, q, *J*=7.2 Hz, H-4), 5.34 (1H, d, *J*=14.7 Hz, Ar–CH_2–N), 4.35

(1H, dd, *J*=8.8, *J*=5.1 Hz, H-1), 4.02 (1H, d, *J*=14.7 Hz, Ar–CH_2–N), 3.76 (3H, s, OCH_3), 1.91 (2H, m, H-α), 1.76 (3H, d, *J*=7.2 Hz, CH_3), 1.50 (2H, m, H-β), 1.23 (2H, m, H-ɣ), 0.87 (3H, t, *J*=7.1 Hz, H-δ). NOE (δ; %): irradiate Me-4 (1.76), observe H-α (1.91; 1.1) and H-4 (5.41; 6.9). ^{13}C NMR ($CDCl_3$) δ: 167.4, 160.6, 159.6, 150.6, 147.2, 134.7, 129.9, 127.6, 127.2, 127.1, 126.8, 120.5, 114.5, 59.7, 55.4, 52.6, 47.6, 35.8, 28.6, 22.5, 19.3, 13.9. Analysis calc. for $C_{24}H_{27}N_3O_3$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.93; H, 6.74; N, 10.18.

1.6.3. Data for anti-***19d***

Mp: 164–166°C (dichloromethane:ethyl acetate). $[\alpha]_D$: +45.9 (0.31, dichloromethane). IR (KBr) ν: 1682, 1609cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 8.25 (1H, dd, *J*=8.0, 1.6 Hz, H-7), 7.72 (1H, ddd, *J*=8.2, 7.1, 1.6 Hz, H-9), 7.52 (1H, dd, *J*=8.2, 1.2 Hz, H-10), 7.48 (1H, ddd, *J*=8.0, 7.1, 1.2 Hz, H-8), 7.22 (2H, d, *J*=8.7 Hz, H-2′ and 6′), 6.80 (2H, d, *J*=8.7 Hz, H-3′ and 5′), 5.72 (1H, s, H-1), 5.41 (1H, q, *J*=7.1 Hz, H-4), 5.25 (1H, s, OH), 5.05 (1H, d, *J*=15.6 Hz, Ar–CH_2–N), 4.44 (1H, d, *J*=15.6 Hz, Ar–CH_2–N), 3.71 (3H, s, OCH_3), 1.83 (3H, d, *J*=7.1 Hz, CH_3). NOE (δ; %): irradiate Me-4 (1.83), observe H-4 (5.41; 6.1) and H-1 (5.72; 3). ^{13}C NMR ($CDCl_3$) δ: 169,3, 159.7, 159.6, 149.7, 146.6, 134.9, 130.2, 127.6, 127.9, 127.0, 126.8, 120.8, 114.5, 79.5, 55.3, 52.8, 47.3, 19.5. Analysis calc. for $C_{20}H_{19}N_3O_4$: C, 65.74; H, 5.24; N, 11.50. Found: C, 65.22; H, 5.20; N, 11.60.

*1.7. (1*S**,4*S**)-1-Isopropyl-2-*p*-methoxybenzyl-4-methyl-2,4-dihydro-1*H*-pyrazino-[2,1-*b*]quinazoline-3,6-dione (±)-*syn-***6d**

Method A: Reaction time 2 h at −78°C and 4 h at 0°C; column chromatography (ethyl acetate:petroleum ether 7:3). Mp: 153–155°C (ethyl ether). IR (KBr) ν: 1682, 1604 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 8.24 (1H, dd, *J*=8.0, 1.2 Hz, H-7), 7.71 (1H, ddd, *J*=7.6 Hz, 7.1, 1.2 Hz, H-9), 7.57 (1H, dd, *J*=7.6, 1.1 Hz, H-10), 7.45 (1H, ddd, *J*=8.0, 7.1, 1.1 Hz, H-8), 7.12 (2H, d, *J*=8.6 Hz, H-2′ and 6′), 6.79 (2H, d, *J*=8.6 Hz, H-3′ and 5′), 5.56 (1H, d, *J*=14.8 Hz, Ar–CH_2–N), 5.34 (1H, q, *J*=7.2 Hz, H-4), 4.11 (1H, d, *J*=9 Hz, H-1), 3.90 (1H, d, *J*=14.8 Hz, Ar–CH_2–N), 3.72 (3H, s, OCH_3), 2.24 (1H, m, H-α), 1.79 (3H, d, *J*=7.2 Hz, CH_3), 1.24 (3H, d, *J*=6.8 Hz, CH(CH_3)$_2$), 1.05 (3H, d, *J*=6.7 Hz, CH(CH_3)$_2$). NOE (δ; %): irradiate Me-4 (1.79), observe H-4 (5.34; 6.2) and H-α (2.24; 3.4). ^{13}C NMR ($CDCl_3$) δ: 167.8, 160.6, 159.2, 150.1, 146.8, 134.5, 129.4, 127.3, 127.1, 126.9, 126.5, 120.2, 114.2, 65.5, 55.1, 52.9, 49.8, 35.9, 20.6, 20.3, 18.5. Analysis calc. for $C_{23}H_{25}N_3O_3$: C, 70.57; H, 6.44; N, 10.73. Found: C, 70.23; H, 6.39; N, 10.58.

*1.8. (1*R,*4*S*)-1-Benzyl-2-*p*-methoxybenzyl-4-methyl-2,4-dihydro-1*H*-pyrazino-[2,1-*b*]quinazoline-3,6-dione (*anti-***7d***) and (1*S,*4*S*)-1-benzyl-2-*p*-methoxybenzyl-4-methyl-2,4-dihydro-1*H*-pyrazino-[2,1-*b*]quinazoline-3,6-dione (*syn-***7d***)*

Method A: Column chromatography (ethyl acetate:petroleum ether 7:3).

1.8.1. Data for anti-***7d***

$[\alpha]_D$: +6.8 (0.34, dichloromethane). IR (NaCl) ν: 1683, 1659, 1610 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 8.14 (1H, dd, *J*=8.0, 1.3 Hz, H-7), 7.65 (1H, ddd, *J*=7.6, 7.0, 1.3 Hz, H-9), 7.58 (1H, dd, *J*=7.6, 1.1, H-10), 7.41 (1H, ddd, *J*=8.0, 7.0, 1.0 Hz, H-8), 7.23 (2H, d, *J*=8.6 Hz, H-2′ and 6′), 7.09 (3H, m, Ph), 6.87 (2H, d, *J*=8.6 Hz, H-3′ and 5′), 6.63 (2H, m, Ph), 5.67 (1H, d, *J*=14.7 Hz, Ar–CH_2–N), 4.68 (1H, 't', *J*=3.5 Hz, H-1), 4.03 (1H, q, *J*=6.7 Hz, H-4), 4.00 (1H, d, *J*=14.7 Hz, Ar–CH_2–N), 3.75 (3H, s, OCH_3), 3.40 (1H, dd, *J*=13.8, 3.5 Hz, H-α), 3.22 (1H, dd, *J*=13.8 Hz, 3.5 Hz, H-α), 1.50 (3H, d, *J*=6.7 Hz, CH_3).

^{13}C NMR ($CDCl_3$) δ: 167.6, 160.2, 159.7, 149.9, 146.8, 134.8, 133.7, 129.9, 129.6, 128.7, 127.9, 127.3, 127.0, 126.8, 126.7, 120.5, 114.6, 59.8, 55.4, 52.1, 46.1, 39.8, 20.6. Analysis calc. for $C_{27}H_{25}N_3O_3$: C, 73.79; H, 5.73; N, 9.56. Found: C, 74.01; H, 5.80; N, 10.00.

1.8.2. Data for syn-***7d***

$[\alpha]_D$: +47.3 (0.66, chloroform). IR (NaCl) ν: 1684, 1662, 1610 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 8.18 (1H, dd, *J*=8.0, 1.3 Hz, H-7), 7.68 (1H, ddd, *J*=7.6, 7.0, 1.3 Hz, H-9), 7.50 (1H, dd, *J*=7.6, 1.0 Hz, H-10), 7.41 (1H, ddd, *J*=8.0, 7.0, 1.0 Hz, H-8), 7.20 (2H, d, *J*=8.6 Hz, H-2′ and 6′), 7.05 (5H, m, Ph), 6.70 (2H, d, *J*=8.6 Hz, H-3′ and 5′), 5.38 (1H, d, *J*=14.7 Hz, Ar–CH_2–N), 5.25 (1H, q, *J*=7.2 Hz, H-4), 4.72 (1H, dd, *J*=7.0, 4.9 Hz, H-1), 3.95 (1H, d, *J*=14.7 Hz, Ar–CH_2–N), 3.66 (3H, s, OCH_3), 3.38 (1H, dd, *J*=13.8, 4.9 Hz, H-α), 3.30 (1H, dd, *J*=13.8, 3.5 Hz, H-α), 1.18 (3H, d, *J*=7.2 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 167.2, 160.1, 159.4, 150.4, 147.2, 135.7, 134.7, 130.0, 129.2, 128.9, 127.8, 127.2, 127.0, 126.9, 126.8, 120.3, 114.4, 60.7, 55.2, 52.3, 47.1, 41.4, 18.4. Analysis calc. for $C_{27}H_{25}N_3O_3$: C, 73.79; H, 5.73; N, 9.56. Found: C, 73.33; H, 5.71; N, 9.21.

*1.9. (1*R,*4*S*)-2-(*p-*Methoxybenzyl)-4-methyl-1-*p-*methylbenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (*anti-***8d***)*

Method A: Starting from **1d**,[20] *syn-* and *anti-***8d** were obtained; column chromatography (CH_2Cl_2:petroleum ether 9:1). Yield: 234 mg (52%). Mp: 167–168°C (CH_2Cl_2:petroleum ether). $[\alpha]_D$: +97.2 (0.43, CH_2Cl_2). IR (KBr) ν: 1682, 1665 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 8.20 (1H, dd, *J*=8.0, 1.3 Hz, H-7), 7.77 (1H, ddd, *J*=8, 7.1, 1.3 Hz, H-9), 7.61 (1H, dd, *J*=8, 1.2 Hz, H-10), 7.47 (1H, ddd, *J*=8.0, 7.1, 1.2 Hz, H-8), 7.27 (2H, d, *J*=8.5 Hz, H-2′ and 6′), 6.93 (2H, d, *J*=7.8 Hz, H-3′′ and 5′′), 6.91 (2H, d, *J*=8.5 Hz, H-3′ and 5′), 6.55 (2H, d, *J*=7.9 Hz, H-2′′ and 6′′), 5.72 (1H, d, *J*=14.6 Hz, Ar–CH_2–N), 4.80 (1H, 't', *J*=3.5 Hz, H-1), 4.06 (1H, q, *J*=6.7 Hz, H-4), 4.02 (1H, d, *J*=14.6 Hz, Ar–CH_2–N), 3.81 (3H, s, OCH_3), 3.42 (1H, dd, *J*=13.9, 3.9 Hz, H-α), 3.27 (1H, dd, *J*=13.8, 3.2 Hz, H-α) 2.26 (3H, s, CH_3–Ar), 1.55 (3H, d, *J*=6.6 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 167.7, 160.3, 160.3, 159.7, 150.2, 146.9, 137.8, 134.8, 130.3, 129.6, 129.5, 129.5, 127.4, 127.0, 126.9, 120.6, 114.6, 59.0, 55.4, 52.2, 46.1, 39.5, 21.2, 20.8. Analysis calc. for $C_{28}H_{27}N_3O_3$: C, 74.15; H, 6.00; N, 9.26. Found: C, 74.31; H; 6.27; N; 9.48.

*1.10. (1*R,*4*S*)-2-(2,4-Dimethoxybenzyl)-4-methyl-1-*p-*methylbenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (*anti-***8e***)*

Method A: Starting from **1e**, *syn-* and *anti-***8e** were obtained; column chromatography (CH_2Cl_2:EtAcO 9:1). Yield: 361 mg (75%). Mp: 127–129°C (ethyl ether). $[\alpha]_D$: +85.6 (0.25, CH_2Cl_2). IR (KBr) ν: 1685, 1666 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 8.16 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.76 (1H, ddd, *J*=7.7, 7.2, 1.5 Hz, H-9), 7.61 (1H, dd, *J*=7.7, 1.2 Hz, H-10), 7.45 (1H, ddd, *J*=8.0, 7.2, 1.2 Hz, H-8), 7.24 (1H, d, *J*=8.9 Hz, H-6′), 6.91 (2H, d, *J*=7.8 Hz, H-3′′ and 5′′), 6.53 (2H, d, *J*=7.8 Hz, H-2′′ and 6′′), 6.48 (1H, dd, *J*=8.9, 2.3 Hz, H-3′), 6.48 (1H, d, *J*=2.3 Hz, H-5′), 5.26 (1H, d, *J*=14.4 Hz, Ar–CH_2–N), 4.82 (1H, 't', *J*=3.9, 3.2 Hz, H-1), 4.24 (1H, d, *J*=14.4 Hz, Ar–CH_2–N), 4.00 (1H, q, *J*=6.6 Hz, H-4), 3.46 (1H, dd, *J*=13.8, 3.9 Hz, H-α), 3.18 (1H, dd, *J*=13.8, 3.2 Hz, H-α) 3.82 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 2.32 (3H, s, CH_3–Ar), 1.48 (3H, d, *J*=6.6 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 167.3, 161.1, 160.3, 159.1, 150.6, 146.9, 137.6, 134.7, 131.7, 130.6, 129.6, 129.4, 126.9, 126.8, 126.6, 120.5, 115.8, 104.7, 98.8, 59.3, 55.6, 55.6, 52.2, 41.6, 40.0, 21.2, 20.8. Analysis calc. for $C_{29}H_{29}N_3O_4$: C, 72.03; H, 6.04; N, 8.69. Found: C, 71.81; H; 6.25; N; 8.48.

*1.11. (1*S*,4*R*)-1,4-Dimethyl-2-*p*-methoxybenzyl-4-*p*-methylbenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione **12d** and (1*S*,4*R*)-1,4-bis(*p*-methylbenzyl)-1,4-dimethyl-2-*p*-methoxybenzyl-2,4-dihydro-1*H*-pyrazino-[2,1-*b*]quinazoline-3,6-dione **20d***

Method B: Starting from *syn*-**3d**, **12d** and **20d** were obtained; column chromatography (ethyl acetate:petroleum ether 6:4).

*1.11.1. Data for **12d***

Mp: 138–140°C (ethyl acetate:petroleum ether). $[\alpha]_D$: −162.2 (0.29, chloroform). IR (KBr) ν: 1683, 1601 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.33 (1H, dd, *J*=7.9, 1.5 Hz, H-7), 7.72 (1H, ddd, *J*=8.2, 7.9, 1.5 Hz, H-9), 7.49 (1H, ddd, *J*=8.2, 7.9, 1.1 Hz, H-8), 7.46 (1H, dd, *J*=7.9, 1.1 Hz, H-10), 6.77 (8H, m, Ar–H), 5.37 (1H, d, *J*=14.8 Hz, Ar–CH_2–N), 4.39 (1H, d, *J*=13.8 Hz, H-α), 4.13 (1H, q, *J*=6.8 Hz, H-1), 3.88 (1H, d, *J*=14.8 Hz, Ar–CH_2–N), 3.79 (3H, s, OCH_3), 3.62 (1H, d, *J*=13.8 Hz, H-α), 2.22 (3H, s, CH_3 (4)), 2.19 (3H, s, CH_3), 1.48 (3H, d, *J*=6.8 Hz, CH_3). NOE (δ; %): irradiate Me-4 (2.22), observe Me-1 (1.48; 4.2), H-α (3.62; 3.5) and H-α (3.79; 3.5). ^{13}C NMR ($CDCl_3$) δ: 168.6, 162.7, 159.4, 152.0, 146.5, 136.3, 134.6, 133.2, 129.7, 129.6, 129.0, 127.1, 127.0, 126.5, 126.9, 121.3, 114.2, 69.2, 55.4, 54.1, 46.9, 40.0, 24.9, 22.4, 21.1. Analysis calc. for $C_{29}H_{29}N_3O_3$: C, 74.50; H, 6.25; N, 8.99. Found: C, 74.04; H, 6.31; N, 8.87.

*1.11.2. Data for **20d***

$[\alpha]_D$: +48.7 (0.27, dichloromethane). IR (NaCl) ν: 1683, 1650, 1610 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.30 (1H, dd, *J*=7.9, 1.5 Hz, H-7), 7.80 (1H, ddd, *J*=7.9, 7.6, 1.5 Hz, H-9), 7.67 (1H, d, *J*=7.6, 1.3 Hz, H-10), 7.52 (1H, ddd, *J*=7.9, 7.9, 1.3 Hz, H-8), 7.30 (2H, d, *J*=8.7z, H-2′ and 6′), 6.90 (2H, d, *J*=8.0 Hz, H-3 and 5 Ar (1)), 6.85 (2H, d, *J*=8.7 Hz, H-3′ and 5′), 6.60 (2H, d, *J*=7.8 Hz, H-3 and 5 Ar (4)), 6.51 (2H, d, *J*=8.0 Hz, H-2 and 6 Ar (1)), 6.40 (2H, d, *J*=7.8 Hz, H-2 and 6 Ar (4)), 5.13 (1H, d, *J*=14.6 Hz, Ar–CH_2–N), 4.35 (1H, d, *J*=14.6 Hz, Ar–CH_2–N), 4.09 (1H, d, *J*=13.7 Hz, H-α^4), 3.85 (3H, s, OCH_3), 3.33 (1H, d, *J*=13.7 Hz, H-α^1), 3.20 (2H, d, *J*=13.7 Hz, H-α and α′), 2.20 (3H, s, CH_3), 2.13 (3H, s, CH_3), 1.54 (3H, s, CH_3 (1)), 1.19 (3H, s, CH_3 (4)). NOE (δ; %): irradiate Me-4 (1.19), observe H-α^4 (3.20; 5), H-α^4 (4.09; 4.7), H–Ar (1) (6.51; 2.8) and H–Ar (1) (6.90; 5.3), irradiate Me-1 (1.54), observe H-α^1 (3.20 and 3.33; 6.4), *N*–CH_2–Ar (4.35; 4.9), H–Ar (4) (6.40; 4.2), H–Ar (4) (6.60; 2.2) and H-2′ and 6′ (7.30; 11.6). ^{13}C NMR ($CDCl_3$) δ: 168.8, 161.9, 158.6, 153.6, 146.2, 137.1, 135.8, 134.3, 133.3, 131.9, 130.9, 129.6, 129.5, 129.4, 129.3, 128.9, 126.8, 126.7, 121.1, 113.2, 67.5, 66.7, 55.4, 47.7, 47.6, 41.1, 30.4, 29.2, 23.9, 21.0. Analysis calc. for $C_{37}H_{37}N_3O_3$: C, 77.73; H, 6.52; N, 7.35. Found: C, 77.60; H, 6.71; N, 7.70.

*1.12. (1*S*,4*R*)-2-Benzyl-1,4-bis(*p*-methylbenzyl)-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione **13c***

Method A: Starting from *syn*-**9c**,[3a] **13c** was obtained after column chromatography (ethyl acetate:petroleum ether 8:2). $[\alpha]_D$: −137 (0.10, chloroform). IR (KBr) ν: 1684, 1648 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.3 (1H, dd, *J*=8.1, 1.1, H-7), 7.7 (1H, ddd, *J*=8.1, 8.1, 1.5 Hz, H-9), 7.5 (1H, dd, *J*=8.1, 1.5 Hz, H-10), 7.5 (1H, ddd, *J*=8.1, 8.1, 1.1 Hz, H-8), 7.25 (3H, m, ArH), 7.0 (2H, d, *J*=8.3 Hz, H-3″,5″), 6.8 (2H, m, ArH), 6.7 (d, *J*=8.3 Hz, 2H, H-3′,5′), 6.6 (d, *J*=8.3 Hz, 2H, H-2″,6″), 6.6 (d, *J*=8.3 Hz, 2H, H-2′,6′), 5.62 (d, *J*=14.9 Hz, 1H, CH_2–*N*), 4.36 (1H, t, *J*=4.2 Hz, H-1), 4.17 (1H, d, *J*=13.8 Hz, CH_2-4), 3.93 (1H, dd, *J*=14.9 Hz, CH_2-*N*), 3.34 (1H, d, *J*=13.8 Hz, CH_2-4), 3.17 (1H, dd, *J*=13.9, 4.1 Hz, CH_2-1), 3.12 (1H, dd, *J*=13.9, 4.3 Hz, CH_2-1), 2.23 (3H, s, CH_3), 2.19 (3H, s, CH_3), 1.42 (3H, s,

CH_3). ^{13}C NMR ($CDCl_3$) δ: 168.7, 162.2, 150.9, 146.4, 138.5, 137.6, 136.1, 134.4, 133.3, 131.3, 129.8, 129.6, 129.1, 129, 128.9, 127.1, 127, 126.4, 121.5, 68.8, 58.8, 47.3, 40.7, 39.8, 21.4, 21.2, 21.1. Analysis calc. for $C_{35}H_{33}N_3O_2$: C, 79.67; H, 6.30; N, 7.96. Found C, 79.98; H, 6.55; N, 7.68.

*1.13. (1*R*,4*S*)-2-Benzyl-4-methyl-1-*p*-methylbenzyl-1-*p*-fluorobenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione* ***14c***

Method A: Starting from *anti*-**9c**,[3a] **14c** (1.2 h at 0°C) was obtained after column chromatography (dichloromethane:ethyl acetate, 9:1). $[\alpha]_D$: +16.6 (0.25, chloroform). IR (NaCl) ν: 1683, 1662, 1609 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.17 (1H, dd, *J*=9.0, 1.4 Hz, H-7), 7.80 (1H, ddd, *J*=7.0, 8.2, 1.4 Hz, H-9), 7.77 (1H, dd, *J*=8.1, 1.1 Hz, H-10), 7.45 (1H, ddd, *J*=8.1, 7.0, 1.1 Hz, H-8), 7.37 (2H, m, ArH), 7.25 (3H, m, ArH), 6.78 (2H, d, *J*=7.9 Hz, H-3 and 5 ArMe), 6.51 (4H, m, ArF), 6.50 (2H, d, *J*=7.9 Hz, H-2 and 6 ArF), 5.08 (1H, d, *J*=15.4 Hz, Ar–CH_2–N), 4.98 (1H, d, *J*=15.4 Hz, Ar–CH_2–N), 4.55 (1H, q, *J*=6.8 Hz, H-4), 3.90 (2H, d, *J*≈14.4 Hz, C_1–CH_2–Ar), 3.53 (1H, d, *J*=14.7 Hz, C_1–CH_2–Ar–F), 3.45 (1H, d, *J*=14.1 Hz, C_1–CH_2–Ar–Me), 2.13 (3H, s, CH_3), 0.73 (3H, d, *J*=6.8 Hz). NOE (δ; %): irradiate Me-4 (0.73), observe H-2 and 6 ArMe (6.50; 0.5) and H-4 (4.55; 7.7). ^{13}C NMR ($CDCl_3$) δ: 168.4, 161.5 (d, *J*=246 Hz), 159.9, 151.9, 146.6, 137.5, 137.0, 134.7, 131.7, 130.7 (d, *J*=8 Hz), 130.4 (d, *J*=3.5 Hz), 130.2, 129.1, 128.5, 127.5, 127.0, 126.9, 126.6, 119.9, 114.9 (d, *J*=21 Hz), 72.7, 51.1, 47.3, 45.7, 44.9, 20.7, 19.1. Analysis calc. for $C_{34}H_{30}N_3O_2F$: C, 76.81; H, 5.68; N, 7.90. Found: C, 76.77; H, 5.43; N, 7.56.

*1.14. (1*S*,4*S*)-2-Benzyl-4-methyl-1-*p*-methylbenzyl-1-*p*-fluorobenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione* ***15c***

Method A: Starting from *anti*-**10c**,[3a] **15c** was obtained after column chromatography (dichloromethane:ethyl acetate, 9:1). $[\alpha]_D$: +38.8 (0.26, chloroform). IR (NaCl) ν: 1674, 1656, 1607 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.20 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.81 (1H, ddd, *J*=8.1, 7.1, 1.5 Hz, H-9), 6.75 (1H, dd, *J*=8.1, 1.5 Hz, H-10), 7.48 (1H, ddd, *J*=8.0, 7.1, 1.5 Hz, H-8), 7.38 (2H, m, ArH), 7.28 (3H, m, ArH), 6.75 (2H, d, *J*=8.2 Hz, H-3 and 5 ArMe), 6.57 (2H, t, *J*=8.8 Hz, H-3 and 5 ArF), 6.49 (2H, d, *J*=8.2 Hz, H-2 and 6 ArMe), 6.42 (2H, dd, *J*=5.5, 8.8 Hz, H-2 and 6 ArF), 5.38 (1H, d, *J*=15.1 Hz, Ar–CH_2–N), 4.68 (1H, d, *J*=15.1 Hz, Ar–CH_2–N), 4.65 (1H, q, *J*=6.8 Hz, H-4), 3.95 (1H, d, *J*=14.2 Hz, C_1–CH_2–Ar–F), 3.89 (1H, d, *J*=14.3 Hz, C_1–CH_2–Ar–Me), 3.58 (1H, d, *J*=14.3 Hz, C_1–CH_2–Ar–Me), 3.38 (1H, d, *J*=14.2 Hz, C_1–CH_2–Ar–F), 2.14 (3H, s, CH_3), 0.89 (3H, d, *J*=6.8 Hz, CH_3). NOE (δ; %): irradiate Me-4 (0.89), observe H-2 and 6 ArF (6.42; 1), H-3 and 5 ArF (6.57; 1) and H-4 (4.65; 8.1). ^{13}C NMR ($CDCl_3$) δ: 168.4, 161.6, 159.8, 151.8, 146.6, 137.7, 136.9, 134.7, 131.8 (d, *J*=8.0 Hz), 131.1, 130.9 (d, *J*=3 Hz), 129.0, 128.7, 128.6, 127.6, 126.9, 126.6, 119.9, 114.9 (d, *J*=21 Hz), 72.9, 51.0, 47.1, 46.6, 44.2, 20.8, 19.9. Analysis calc. for $C_{34}H_{30}N_3O_2F$: C, 76.81; H, 5.68; N, 7.90. Found: C, 76.69; H, 5.48; N, 7.58.

*1.15. (4*S*)-2-Benzyl-1,1-diallyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione* ***16c***

Method A: Starting compound **1c**, reaction time 1 h; column chromatography: dichloromethane:ethyl acetate (9:1) affording **16c**, besides both C-1 allyl isomers.[3a] $[\alpha]_D$=+8.7 (0.25, chloroform). IR ν: 1682, 1655 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.23 (1H, dd, *J*=8.1, 1.5 Hz, H-7), 7.74 (1H, ddd, *J*=8.1, 8.1, 1.5 Hz, H-9), 7.63 (1H, dd, *J*=8.1, 1.2 Hz, H-10), 7.45 (1H, ddd, *J*=8.1, 8.1, 1.2 Hz, H-8), 7.44 (2H, m, ArH-3 and 5), 7.29 (3H, m, ArH-2, 4 and 6), 5.32 (1H, d, *J*=6.8 Hz, H-4), 5.3 (2H, m, Hβ and β′), 5.09 (1H, d,

J=15.3 Hz, N–CH_2–Ar), 4.89 (1H, dd, *J*=10.3, 1.7 Hz, Hγ′$_c$), 4.82 (1H, dd, *J*=10.6, 1.7 Hz, Hγ$_c$), 4.76 (1H, dd, *J*=17.1, 1.7 Hz, Hγ′$_t$), 4.73 (1H, dd, *J*=17.1, 1.1 Hz, Hγ$_t$), 4.60 (1H, d, *J*=15.3 Hz, N–CH_2–Ar), 3.22 (1H, dd, *J*=14.5, 7.3 Hz, Hα′), 3.07 (1H, dd, *J*=14.1, 7.8 Hz, Hα), 2.88 (1H, dd, *J*=14.5, 6.8 Hz, Hα′), 2.72 (1H, dd, *J*=14.1, 6.9 Hz, Hα), 1.69 (3H, d, *J*=6.8 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 168.3, 160.2, 151.9, 147.1, 137.8, 134.5, 131.5, 130.6, 128.5, 128.4, 127.5, 127.1, 126.8, 126.5, 120.8, 120.5, 119.8, 70.7, 51.2, 45.5, 44.6, 43.9, 21.4. Analysis calc. for $C_{25}H_{25}N_3O_2$: C, 75.16; H, 6.31; N, 10.52. Found C, 75.29; H, 6.46; N, 10.20.

*1.16. 2-Benzyl-1,1-bis(*p*-methylbenzyl)-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione, (±)-**17c** and (1*S**,4*R**)-2-benzyl-1,4-bis(*p*-methylbenzyl)-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (±)-**13c***

Method A: Starting compound **1c**, reaction time 12 h; column chromatography: dichloromethane:ethyl acetate (9:1) affording (±)-**13c** (12%), (±)-**17c** (7%), besides *anti*-**9c**[3a] and (±)-*syn*-**9c**.

*1.16.1. Data for (±)-*syn-***9c***

Mp: 157–160°C (ethyl ether). For spectroscopic data see Martín-Santamaría[3a] Analysis calc. for $C_{27}H_{25}O_2N_3$: C, 76.57; H, 5.95; N, 9.92. Found C, 76.19; H, 6.26; N, 9.12.

*1.16.2. Data for (±)-**17c***

IR (KBr) ν: 1684, 1648 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 8.19 (1H, dd, *J*=8.0, 1.0 Hz, H-7), 7.78 (1H, dd, *J*=8.0, 1.5 Hz, H-10), 7.76 (1H, ddd, *J*=8.0, 8.0, 1.0 Hz, H-9), 7.5 (1H, ddd, *J*=8.0, 8.0, 1.5 Hz, H-8), 7.35 (2H, m, ArH), 7.25 (3H, m, ArH), 6.73 (2H, d, *J*=8.0 Hz, H-3′,5′), 6.72 (2H, d, *J*=8.0 Hz, H-3′′,5′′), 6.45 (2H, d, *J*=8.0 Hz, H-2′,6′), 6.41 (2H, d, *J*=8.0 Hz, H-2′′, 6′′), 5.21 (1H, d, *J*=15.0 Hz, N–CH_2–Ar), 4.84 (1H, d, *J*=15.0 Hz, N–CH_2–Ar), 4.79 (1H, q, *J*=6.8 Hz, H-4), 3.93 (1H, d, *J*=14.5 Hz, CH_2-1), 3.92 (1H, d, *J*=14.1 Hz, CH_2-1), 3.53 (1H, d, *J*=14.5 Hz, CH_2-1), 3.4 (1H, d, *J*=14.1 Hz, CH_2-1), 2.11 (6H, s, 2CH_3–Ar), 0.8 (3H, d, *J*=6.8 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 168.6, 160.2, 152.3, 146.9, 137.7, 136.7, 136.6, 134.6, 131.9, 131.4, 130.2, 129.1, 129, 128.9, 128.4, 128.1, 127.9, 127.1, 126.8, 126.5, 120.2, 72.9, 51.3, 47.5, 46.6, 45.1, 21, 20.9, 19.6. Analysis calc. for $C_{35}H_{33}N_3O_2$: C, 79.67; H, 6.30; N, 7.96. Found C, 79.82; H, 6.49; N, 7.63.

*1.16.3. Data for (±)-**13c***

Mp: 137–140°C. Spectral data identical to (−)-**13c** described above. Analysis calc. for $C_{35}H_{33}O_2N_3$: C, 79.67; H, 6.30; N, 7.96. Found C, 79.31; H, 6.60; N, 7.60.

*1.17. (4S)-4-Methyl-1,1,2-tribenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione, **18c***

Method C: Column chromatography: dichloromethane:ethyl acetate (9:1). $[\alpha]_D$=+19 (0.25, chloroform). IR (KBr) ν: 1687, 1660 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 8.17 (1H, dd, *J*=8.1, 1.5 Hz, H-7), 7.8 (1H, ddd, *J*=8.1, 8.1, 1.5 Hz, H-9), 7.73 (1H, dd, *J*=8.1, 1.5 Hz, H-10), 7.48 (1H, ddd, *J*=8.1, 8.1, 1.5 Hz, H-8), 7.35 (2H, m, ArH), 7.23 (3H, m, ArH), 6.95 (6H, m, ArH), 6.56 (4H, m, ArH), 5.18 (1H, d, *J*=15.1 Hz, N–CH_2–Ar), 4.89 (1H, d, *J*=15.1 Hz, N–CH_2–Ar), 4.69 (1H, q, *J*=6.8 Hz, H-4), 3.98 (1H, d, *J*=14.2 Hz, CH_2-1), 3.96 (1H, d, *J*=14.6 Hz, CH_2′-1), 3.59 (1H, d, *J*=14.6 Hz, CH_2′-1), 3.45 (1H, d, *J*=14.2 Hz, CH_2-1), 0.77 (3H, d, *J*=6.8 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 168.4, 160.0, 151.9, 146.6, 137.5, 135.0, 134.6, 134.5, 130.3, 129.0, 128.9, 128.4, 128.3, 128.2, 127.5, 127.1, 127.0, 126.9, 126.8, 126.1, 119.9,

72.4, 51.1, 47.3, 46.8, 45.3, 19.4. Analysis calc. for $C_{33}H_{29}N_3O_2$: C, 79.33; H, 5.85; N, 8.41. Found C, 79.07; H, 5.69; N, 8.36.

*1.18. Oxidation of **1c** or **1d** with HCOOH–C/Pd. General procedure*

Compound **1c** or **1d** (0.3 mmol), 10 mg C/Pd 10% and 5 ml of formic acid (95%) were maintained at 50°C for 24 h (**1c**) or 6 h (**1d**) and filtered. After addition of 20 ml of CH_2Cl_2, the organic layer was washed with water, dried over anhydrous Na_2SO_4 and concentrated. Recrystallization (**1c**) led to **21c** and column chromatography (**1d**) (ethyl acetate:methanol 95:5) afforded 41 mg (40%) **21d** and 42 mg (41%) *syn*-**19d**.

*1.19. (4S)-2-Benzyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-1,3,6-trione **21c***

Yield: 287 g (87%). Mp: 202–204°C ($CHCl_3$:hexane 1:4). $[\alpha]_D$: −2.7 (0.25, CH_2Cl_2). IR (KBr) ν: 1742, 1685, 1590 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.28 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 8.00 (1H, dd, *J*=8.0, 1.2 Hz, H-10), 7.85 (1H, ddd, *J*=8.0, 8.0, 1.5 Hz, H-9), 7.60 (1H, ddd, *J*=8.0, 8.0, 1.2 Hz, H-8), 7.45 (2H, m, Ph), 7.25 (3H, m, Ph), 5.58 (1H, q, *J*=7.0 Hz, H-4), 5.20 (1H, d, *J*=13.6 Hz, Ph–CH_2–N), 5.10 (1H, d, *J*=13.6 Hz, Ph–CH_2–N), 1.65 (3H, d, *J*=7.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 168.4, 159.4, 157.0, 146.5, 138.6, 135.5, 135.3, 129.9, 129.7, 129.5, 128.8, 128.4, 127.0, 121.8, 52.7, 44.7, 21.1. MS (70 eV), m/z (%): 334 ($[M+1]^+$, 36), 333 (M^+, 100), 305 (28), 304 (11), 214 (10), 171 (11), 146 (23), 145 (12), 132 (26), 129 (12), 117 (16), 106 (28), 102 (14), 91 (36), 77 (17), 70 (10), 65 (20). Analysis calc. for $C_{19}H_{15}N_3O_3$: C, 68.46; H, 4.53; N, 12.60. Found: C, 68.32; H, 4.47; N, 12.67.

*1.20. (4S)-2-*p*-Methoxybenzyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-1,3,6-trione **21d***

Mp: 75°C (ethyl acetate:methanol). $[\alpha]_D$: +9.6 (0.25, CH_2Cl_2). IR (KBr) ν: 1741, 1687, 1610 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.30 (1H, dd, *J*=8.3, 1.5 Hz, H-7), 8.01 (1H, dd, *J*=8.2, 1.2 Hz, H-10), 7.85 (1H, ddd, *J*=8.2, 7.2, 1.5 Hz, H-9), 7.63 (1H, ddd, *J*=8.3, 7.2, 1.2 Hz, H-8), 7.43 (2H, d, *J*=8.8 Hz, H-2′and 6′), 6.81 (2H, d, *J*=8.8 Hz, H-3′ and 5′), 5.58 (1H, q, *J*=7.0 Hz, H-4), 5.15 (1H, d, *J*=13.6 Hz, Ar–CH_2–N), 5.05 (1H, d, *J*=13.6 Hz, Ar–CH_2–N), 3.75 (3H, s, OCH_3), 1.66 (3H, d, *J*=7.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 168.4, 159.6, 159.4, 156.7, 146.5, 138.5, 135.4, 131.1, 129.9, 129.6, 127.5, 126.9, 121.7, 113.8, 55.5, 52.8, 44.4, 21.1. Analysis calc. for $C_{20}H_{17}N_3O_4$: C, 66.11; H, 4.72; N, 11.56. Found: C, 66.43; H, 4.51; N, 11.68.

*1.21. (1S,4S)-1-Hydroxy-4-methyl-2-*p*-methoxybenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (*syn-***19d***)*

Mp: 102–104°C (ethyl acetate:methanol). $[\alpha]_D$: +34.4 (0.34, CH_2Cl_2). IR (KBr) ν: 1682, 1611 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.26 (1H, dd, *J*=8.1, 1.5 Hz, H-7), 7.77 (1H, ddd, *J*=8.3, 7.1, 1.5 Hz, H-9), 7.67 (1H, dd, *J*=8.3, 1.2 Hz, H-10), 7.51 (1H, ddd, *J*=8.1, 7.1, 1.2 Hz, H-8), 7.39 (2H, d, *J*=8.7 Hz, H-2′ and 6′), 6.84 (2H, d, *J*=8.7 Hz, H-3′ and 5′), 5.57 (1H, d, *J*=3.5 Hz, H-1), 5.42 (1H, q, *J*=7.2 Hz, H-4), 5.26 (1H, d, *J*=3.5 Hz, OH), 5.16 (1H, d, *J*=14.1 Hz, Ar–CH_2–N), 4.47 (1H, d, *J*=14.1 Hz, Ar–CH_2–N), 3.77 (3H, s, OCH_3), 1.53 (3H, d, *J*=7.2 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 166.3, 159.6, 159.3, 150.2, 146.0, 135.1, 130.5, 128.5, 128.0, 127.2, 127.1, 120.9, 114.0, 74.4, 55.5, 52.8, 44.1, 17.5. MS (70 eV), m/z (%): 365 (M^+, 1), 364 (3), 363 (14), 349 (6), 335 (7), 258 (11), 230 (7), 229 (23), 228 (7), 214 (6), 201 (14), 191 (9), 162 (25), 146 (18), 136 (53), 135 (16), 129 (9), 121 (100), 102 (10), 91 (16), 78 (16), 77 (29),

65 (11), 60 (36), 57 (63). Analysis calc. for $C_{20}H_{19}N_3O_4$: C, 65.74; H, 5.24; N, 11.50. Found: C, 65.34; H, 5.14; N, 11.69.

*1.22. Catalytic hydrogenation of **1c** in acidic medium: (4S)-2-benzyl-4-methyl-2,4,7,8,9,10-hexahydro-1H-pyrazino[2,1-b]quinazoline-3,6-dione **22***

Compound **1c** (350 mg, 1.1 mmol), 100 mg of C/Pd 10% and 1 ml of formic acid (95%) in methanol (50 ml) were hydrogenated at 33 psi for 14 h. The reaction mixture was filtered and concentrated. Column chromatography (ethyl acetate:methanol 95:5) afforded 192 mg (55%) of **22**. Mp: 128–129°C (ethyl acetate:methanol). $[\alpha]_D$: +31.8 (0.25, CH_2Cl_2). IR (KBr) ν: 1666, 1605 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.27 (5H, m, Ph), 5.37 (1H, q, *J*=7.1 Hz, H-4), 4.79 (1H, d, *J*=14.5 Hz, Ph–CH_2–N), 4.70 (1H, d, *J*=14.5 Hz, Ph–CH_2–N), 4.35 (1H, d, *J*=17.0 Hz, H-1), 4.15 (1H, d, *J*=17.0 Hz, H-1), 2.46 (4H, m, H-7 and 10), 1.70 (4H, m, H-8 and 9), 1.53 (3H, d, *J*=7.1 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 167.2, 160.0, 159.3, 148.5, 134.9, 129.0, 128.2, 128.1, 120.4, 51.7, 49.4, 48.6, 31.2, 22.2, 21.9, 21.4, 16.9. MS (70 eV), m/z (%): 324 ($[M+1]^+$, 71), 323 (M^+, 91), 233 (16), 232 (100), 218 (25), 204 (17), 191 (10), 190 (35), 189 (30), 164 (46), 91 (56), 79 (16), 77 (13), 65 (20), 56 (11). Analysis calc. for $C_{19}H_{21}N_3O_2$: C, 70.56; H, 6.54; N, 12.99. Found: C, 70.19; H, 6.42; N, 13.05.

*1.23. (4S)-4-Methyl-2,4-dihydro-1H-pyrazino[2,1-b]quinazoline-3,6-dione **1a***

Method A: **1e** (100 mg, 0.26 mmol), 2.6 ml of TFA (0.1 M) and 0.1 ml of anisole were refluxed for 14 h at 80°C, extracted with $CHCl_3$, dried (Na_2SO_4) and concentrated. Column chromatography (ethyl acetate:methanol 95:5) afforded (+)-**1a** (41 mg; 68%) and traces of **21a** (4 mg, 6%).

Method B: A solution of **1d** (0.5 mmol) in 7 ml acetonitrile:water (5:2) and CAN (0.6 g, 1.1 mmol) was stirred 30 min at rt. The reaction mixture was extracted with chloroform, dried (Na_2SO_4) and concentrated. Column chromatography (ethyl acetate:methanol, 95:5) afforded *syn*-**19d** (10 mg, 7%), (+)-**1a** (43 mg, 38%) and *syn*-**19a** (19 mg, 19%).

*1.23.1. Data for (+)-**1a***

Mp: 207–210°C (ethyl acetate:methanol). $[\alpha]_D$: +42.8 (0.26, $CHCl_3$). IR (KBr) ν: 1675, 1603 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.26 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.74 (1H, ddd, *J*=8.1, 8.1, 1.5 Hz, H-9), 7.69 (1H, d, *J*=4.9 Hz, NH), 7.61 (1H, dd, *J*=8.1, 1.2 Hz, H-10), 7.47 (1H, ddd, *J*=8.1, 8.1, 1.2 Hz, H-8), 5.41 (1H, q, *J*=7.1 Hz, H-4), 4.66 (1H, d, *J*=16.8 Hz, H-1), 4.48 (1H, dd, *J*=16.8, 4.9 Hz, H-1), 1.63 (3H, d, *J*=7.1 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 170.6, 160.3, 147.7, 147.2, 135.0, 127.4, 127.1, 127.0, 120.5, 51.9, 45.1, 17.0. Analysis calc. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.69; H, 4.82; N, 18.50.

*1.24. (4S)-4-Methyl-2,4-dihydro-1H-pyrazino[2,1-b]quinazoline-1,3,6-trione **21a***

^1H NMR ($CDCl_3$) δ: 8.31 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.87 (1H, ddd, *J*=8.2, 7.1, 1.5 Hz, H-9), 7.71 (1H, dd, *J*=8.2, 1.2 Hz, H-10), 7.59 (1H, ddd, *J*=8.0, 7.1, 1.2 Hz, H-8), 5.42 (1H, q, *J*=7.2 Hz, H-4), 1.7 (3H, d, *J*=7.2 Hz, CH_3). (NH not observed). ^{13}C NMR ($CDCl_3$) δ: 169.3, 159.8, 148.7, 145.6, 135.2, 135.0, 127.4, 126.5. 125.6, 119.6, 51.8, 16.1.

*1.25. (1*S*,4*S*)-1-Hydroxy-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (*syn-***19a***)*

Mp: 200–203°C (ethyl acetate:methanol). $[\alpha]_D$: +80.3 (0.18, CH_2Cl_2:methanol (1:1)). IR (KBr) ν: 1698, 1670, 1610 cm^{-1}. ^1H NMR ($CDCl_3$:CD_3OD) δ: 8.07 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.61 (1H, ddd, *J*=8.0, 8.0, 1.5 Hz, H-9), 7.49 (1H, d, *J*=8.0 Hz, H-10), 7.35 (1H, ddd, *J*=8.0, 8.0, 1.2 Hz, H-8), 5.46 (1H, s, H-1), 5.06 (1H, q, *J*=7.1 Hz, H-4), 1.62 (3H, d, *J*=7.1 Hz, CH_3). ^{13}C NMR ($CDCl_3$:MeOD) δ: 171.8, 160.3, 149.2, 146.6, 134.6, 127.4, 126.7, 126.3, 120.1, 75.5, 52.6, 18.5. MS (70 eV), m/z (%): 246 ($[M+1]^+$, 11), 245 (M^+, 30), 230 (14), 229 (92), 228 (22), 227 (M-18, 100), 175 (12), 174 (77), 173 (14), 172 (11), 171 (17), 146 (30), 145 (18), 144 (18), 132 (13), 131 (13), 130 (32), 129 (23), 121 (55), 118 (13), 117 (31), 116 (14), 90 (26), 77 (35), 76 (61), 75 (34), 63 (24), 60 (89). Analysis calc. for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.62; H, 4.50; N, 17.21.

*1.26. Oxidation of **1d** with DDQ. General procedure*

Compound **1d** (175 mg, 0.5 mmol) and 114 mg (0.5 mmol) of DDQ in 9.5 ml of CH_2Cl_2:water (9:0.5) were stirred at rt for 3 h, filtered, washed with water, dried (Na_2SO_4) and concentrated. Column chromatography (CH_2Cl_2:ethyl acetate, 9:1) gave 65 mg (38%) of recovered **1d**, 20 mg (18%) of *syn*-**19d**, 8 mg (7%) of *anti*-**19d** and 4 mg (4%) of **21d**.

*1.27. (1*S*,4*S*)-4-Methyl-1-*p*-methylbenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (*syn-***8a***)*

A mixture of compound *anti*-**8e** (48 mg, 0.1 mmol) in 1 ml of TFA (0.1 M) and 0.05 ml of anisole was refluxed for 7 h at 80°C, dissolved in CH_2Cl_2, extracted with 1 N $NaHCO_3$, dried (Na_2SO_4) and concentrated. Column chromatography (ethyl acetate:petroleum ether 7:3) afforded *syn*-**8a** (32 mg; 96%). Mp: 221–222°C (ether). $[\alpha]_D$: +23.4 (0.16, CH_2Cl_2). IR (KBr) ν: 1682, 1598 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.30 (1H, dd, *J*=8.0, 1.0 Hz, H-7), 7.81 (1H, ddd, *J*=7.6, 7.1, 1.0 Hz, H-9), 7.70 (1H, dd, *J*=7.6, 1.1 Hz, H-10), 7.52 (1H, ddd, *J*=8.0, 7.1, 1.1 Hz, H-8), 7.16• (2H, d *J*=9.1 Hz, H-3′′ and 5′′), 7.13• (2H, d, *J*=9.1 Hz, H-2′′ and 6′′), 6.62 (1H, d, *J*=2.8 Hz, NH), 5.26 (1H, q, *J*=7.1 Hz, H-4), 4.78 (1H, dd, *J*=9.9, 3.7 Hz, H-1), 3.44 (1H, dd, *J*=13.5, 3.7 Hz, H-α), 3.11 (1H, dd, *J*=13.5, 9.9 Hz, H-α), 2,33 (3H, s, CH_3–Ar), 1.50 (3H, d, *J*=7.1 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 168.8, 160.6, 149.9, 147.3, 137.6, 135.0, 132.2, 130.0, 129.6, 127.3, 127.0, 126.9, 120.3, 58.2, 51.9, 43.9, 21.2, 19.0. Analysis calc. for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.60. Found: C, 71.72; H, 5.94; N, 12.25.

*1.28. (1*R*,4*S*)-4-Methyl-1-*p*-methylbenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (*anti-***8a***)*

A solution of *anti*-**8d** (80 mg, 0.18 mmol) in 7 ml acetonitrile:water (5:2) and CAN (210 mg, 0.4 mmol) was stirred for 20 min at rt. The reaction mixture was extracted with chloroform, dried (Na_2SO_4) and concentrated. Column chromatography (ethyl acetate:petroleum ether, 6:4) afforded *anti*-**8a** (20 mg, 34%; 72% based on recovered starting compound. Mp: 187–188°C (ether). $[\alpha]_D$: +102.5 (0.04, $CHCl_3$). IR (KBr) ν: 1684 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.29 (1H, dd, *J*=8.1, 1.2 Hz, H-7), 7.80 (1H, ddd, *J*=8.0, 7.8, 1.2 Hz, H-9), 7.75 (1H, dd, *J*=7.8, 1.0 Hz, H-10), 7.53 (1H, ddd, *J*=8.0, 8.1, 1.0 Hz, H-8), 7.20 (4H, d *J*=8.7 Hz, H–Ar), 5.84 (1H, s, NH), 5.47 (1H, q, *J*=7.1 Hz, H-4), 4.77 (1H, dd, *J*=10.5, 3.7 Hz, H-1), 4.08 (1H, dd, *J*=14.4, 3.7 Hz, H-α), 2.93 (1H, dd, *J*=14.4, 10.5 Hz, H-α), 2.37 (3H, s, CH_3–Ar), 1.61 (3H, d, *J*=7.1 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 168.9, 160.2, 149.6, 146.8, 137.5, 134.6, 132.0, 130.0,

129.0, 127.4, 127.3, 126.8, 120.4, 53.9, 52.0, 37.5, 21.0, 16.8. Analysis calc. for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.60. Found: C, 71.77; H, 5.56; N, 12.27.

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