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Cyclisation of (4*S*)-4-methyl-2-phenethyl-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazoline-3,6-dione derivatives via *N*-acyliminium ions

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Abstract—Enantiomerically pure 1-methylene and 1-oxo derivatives (compounds **4** and **10**, respectively) of compounds **1** were obtained and studied as precursors of *N*-acyliminium ions. 1-Substituted-1-hydroxyderivatives, obtained by regioselective *syn*-addition of organometallics to compounds **10** gave the desired species under acid treatment while compounds **4** did not. *N*-Phenethyl substituted *N*-acyliminium ions gave isoquino[1′,2′:3,4]pyrazino[2,1-*b*]quinazoline-8,11-diones through a Pictet–Spengler-type cyclisation.

1. Introduction

N-Acyliminium ions have highly versatile reaction characteristics which are reflected in the impressive scope of their synthetic applications. Both inter- and intramolecular carbon–carbon bond forming reactions of these ions have been comprehensively reviewed, and their application in cyclisations onto olefins or arenes is in continuous expansion.[1–6] System **1** is used in nature as a scaffold for constrained peptidomimetics, as demonstrated by the structure of several fungal metabolites including glyantrypine,[7] the fumiquinazolines,[8] the fiscalins[9] and *N*-acetylardeemin.[10,11]

We have previously shown that compounds **2** and **3**, obtained by oxidation with hypervalent iodine reagents[12–14] or radical bromination[15] of compounds **1**, behave as glycine templates and generate *N*-acyliminium ions **I** (Scheme 1a). Taking into account that *N*,*N*′-disubstituted-3-methylenepiperazine-2,5-diones[16] are efficient precursors of iminium ions such as **II** by protonation of the double bond (Scheme 1b), we report herein a study into the generation of tertiary iminium cations from 1-methylene derivatives **4**, which are readily accessible through Mannich–Hofmann reactions on compounds **1**. We also report the formation of these species by acid treatment of 1-substituted 1-hydroxy derivatives, obtained by addition of organometallic reagents to 1-oxo compounds **10**. The 2-phenethyl derivatives deserve special interest as they are model compounds able to trap the above-mentioned intermediates through Pictet–Spengler-type reactions.

2. Results and discussion

We have previously described[17] that the 1-methylene-2-methyl derivative (−)-**4a** dimerised to the self-coupling product (−)-**5** when treated with trifluoroacetic acid through a process that implies the protonation at N(11) to give the iminium ion **III**, but the 2-benzyl analogue (−)-**4b** was recovered unaltered after this treatment. This difference in behaviour could be explained if the bulk of the benzyl substituent prevents the C–C coupling reaction to give **5** (Scheme 2). Looking for more adequate analogues to trap the alternative iminium ion **IV** and thus form a six-membered ring,[14] we studied this reaction with the 2-phenethyl derivative (−)-**4c**.

Compound (−)-**4c** could be quantitatively obtained in the Mannich–Hofmann reaction of (−)-**1c** when the unreacted Mannich product (−)-**6c** was submitted to subsequent elimination (its enantiomeric purity was corroborated by chiral HPLC on a Chiracel OD). However, on prolonged acid treatment of **4c** in refluxing trifluoroacetic or concentrated sulfuric acid at room temperature, the expected cyclisation product was not

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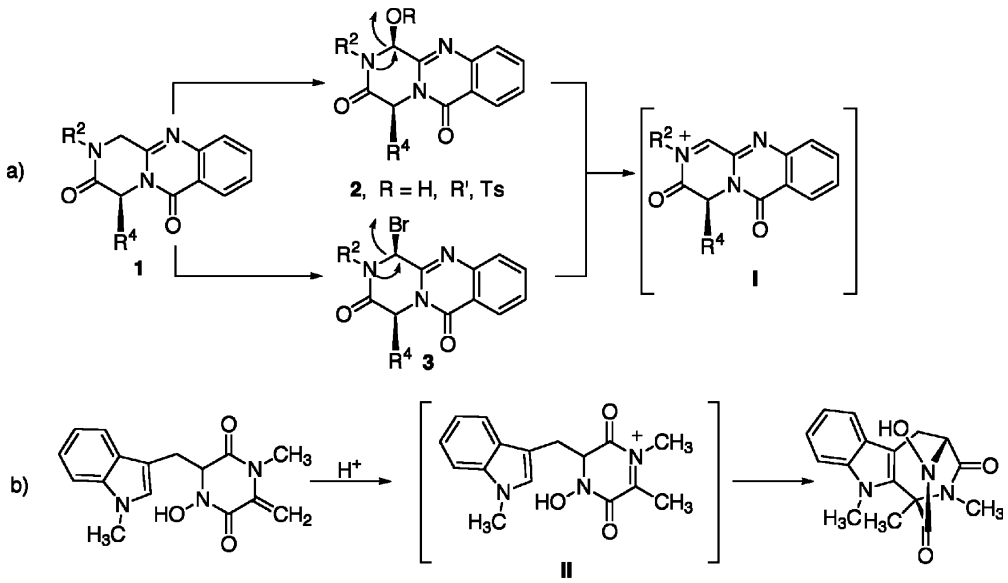
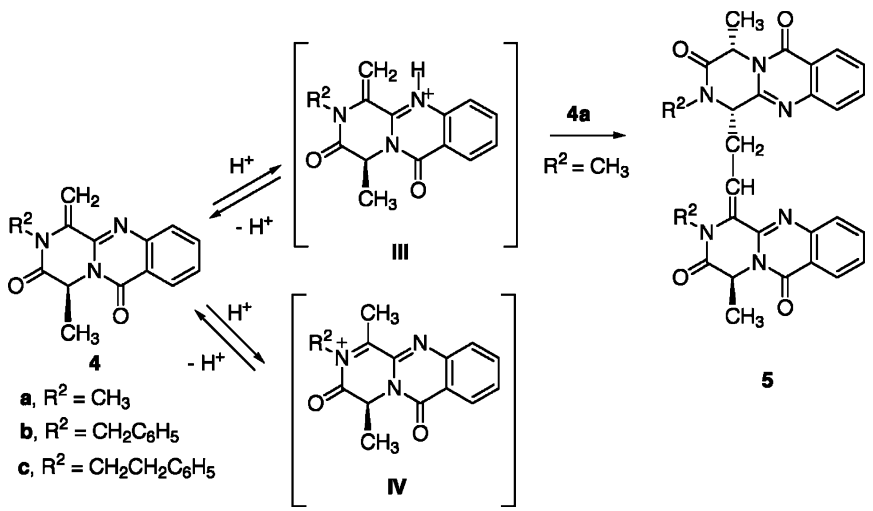


Scheme 1.

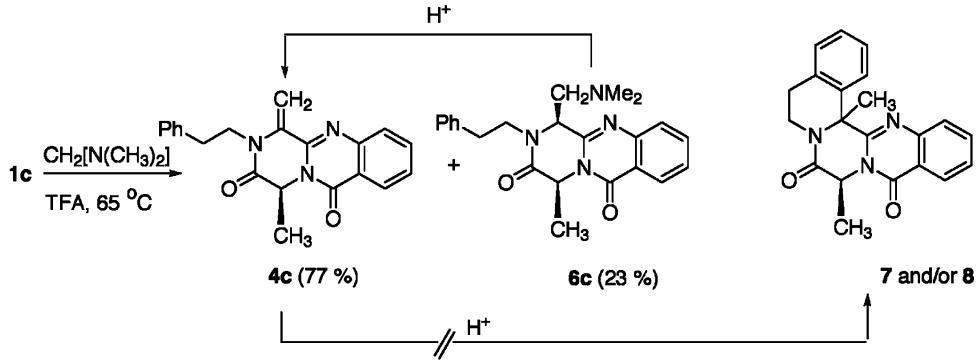


Scheme 2.

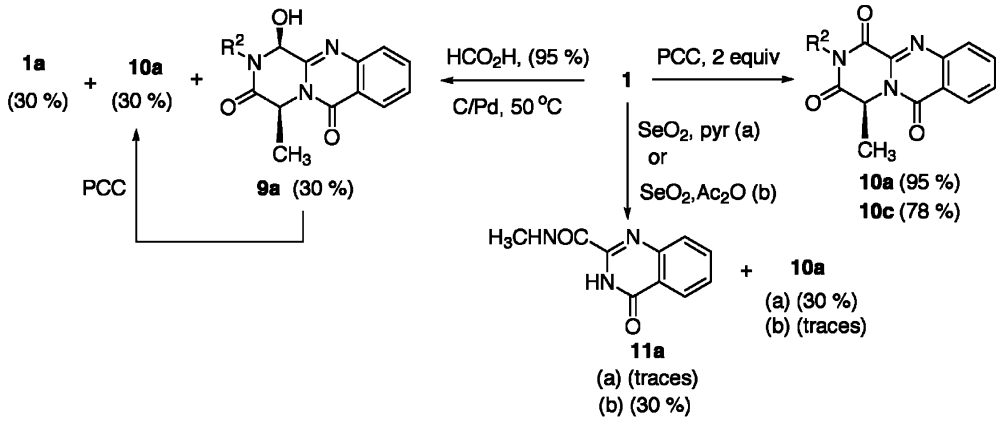
formed **7** and/or **8** and the unreacted starting material was returned (**7** and/or **8**, Scheme 3). We concluded that either the corresponding *N*-acyliminium ion **IV** did not form or the rate of proton elimination was faster than the rate of the Pictet–Spengler-type cyclisation.

Since 1-hydroxy (alkoxy or tosyloxy) derivatives **2**, as other simpler *N*-(1-hydroxy alkyl)amides,[18] generate *N*-acyliminium species (**I**, Scheme 1), we extended this chemistry to form tertiary *N*-acyliminium cations[19] from 1-hydroxy-1-alkyl(aryl) derivatives. In order to obtain the 1-oxo precursors, we studied different oxidation methods with the model compound **1a**. Thus, given the easy oxidation of the 1-formyl derivative, as observed in the attempted reductive *N*(2)-debenzylation of compound **1b** in formic acid,[20] we treated **1a** under the same reaction conditions and obtained a 1:1 mixture of **9a** and **10a** (Scheme 4). Although unreacted **1a** was easily recovered and **9a** was further oxidised with PCC to **10a**, this method was rejected because it is tedious and time consuming. The treatment of **1a** with selenium dioxide in acetic anhydride[21] gave a substantial amount of the decomposition product **11a**, while the reaction in pyridine[22] led to **10a** in low yield. Finally, **10a** was obtained as the sole reaction product in 95% yield by direct treatment of **1a** with two equivalents of PCC. This procedure was then applied to obtain the desired compound **10c** (78%) with e.e. >98%, as determined by ^{1}H NMR spectroscopy using europium(III) [tris(3-heptafluoropropyl hydroxymethylene-(+)-camphorate] as a chiral reagent.

Organometallic additions to compounds **1** and **4** take place at the C(3) carbonyl group,[23] but in the case of compounds **10** these reactions were expected to give adducts on the more electrophilic C(1) carbonyl group. In fact, addition of organolithium and Grignard reagents to **10a** was diastereoselective giving the 1-



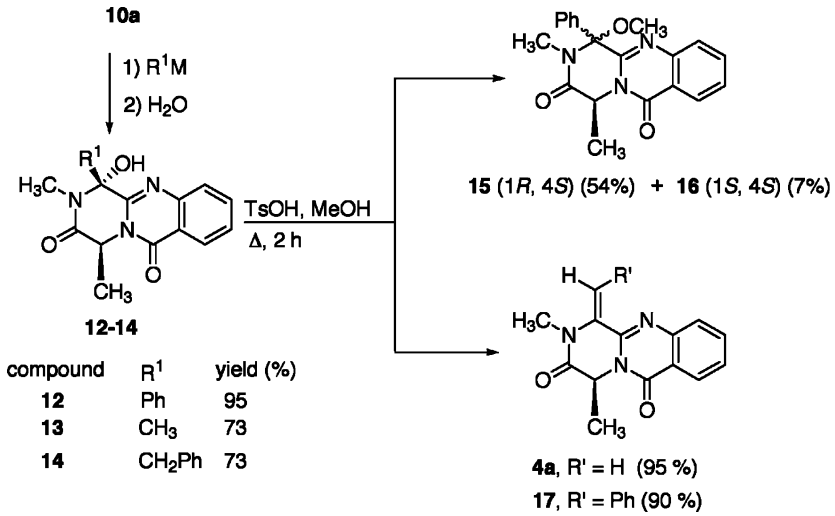
Scheme 3.



Scheme 4.

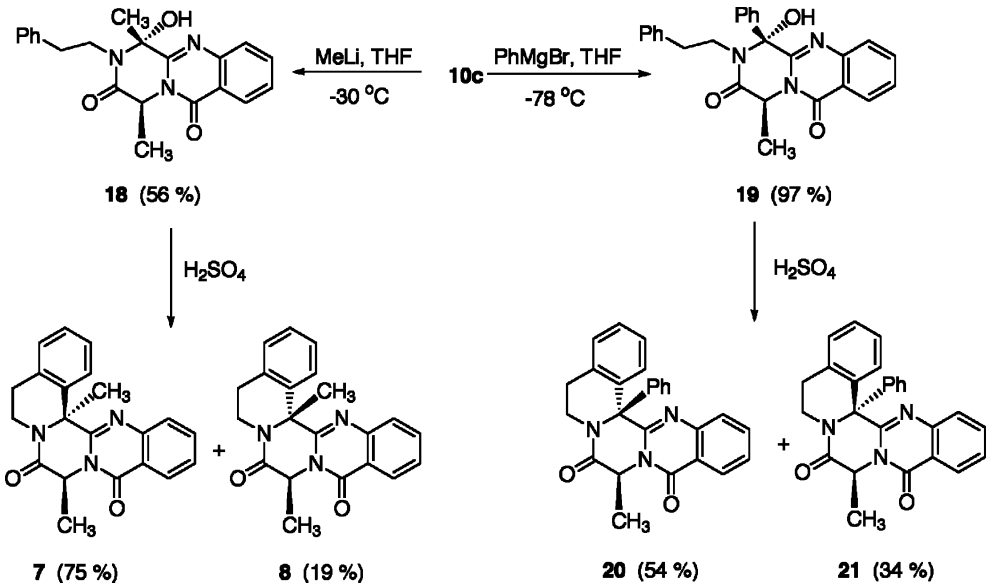
hydroxy derivatives **12**–**14** as 1,4-*syn*-isomers according to NOESY experiments (Scheme 5). The *syn*-selectivity of the Grignard additions to compounds **10** has no precedent in the literature. First assays confirmed that these compounds are effective precursors of tertiary *N*-acyliminium ions in acid media. Thus, treatment of **12** with *p*-toluenesulfonic acid in methanol at room temperature gave the solvolysis products (1*R*,4*S*)-**15** and (1*S*,4*S*)-**16** derivatives in a 8:1 relationship, showing the asymmetric induction by the C(4)-substituent in the addition of methanol as a nucleophile. Under the same conditions, analogues **13** and **14** gave the 1-methylene compounds **4a** and **17** by proton elimination.

We next followed the same protocol using the *N*-phenethyl analogue **10c** to obtain **18** (56%) and **19** (97%) through regio- and diastereoselective *syn*-additions (Scheme 6). Treatment of these compounds with



compound	R^1	yield (%)
12	Ph	95
13	CH_3	73
14	CH_2Ph	73

Scheme 5.



Scheme 6.

sulfuric acid at room temperature afforded the desired cyclised products **7**, **8**, **20** and **21**, whose stereochemistry were unequivocally assigned by NOESY experiments. The enantiomeric purity of these compounds was confirmed by chiral HPLC, in comparison with racemic samples. In the case of **18**, the *syn*-isomer was the major product (diastereomeric ratio **7**/**8** = 4:1), while for **19**, the *anti*-isomer predominated (diastereomeric ratio **20**/**21** = 3:2).

In conclusion, PCC oxidation of compounds **1** with adequate 2-aryl (or heteroaryl)alkyl substituents, followed by organometallic addition and acid treatment, could be used to generate tertiary *N*-acyliminium ions, useful as intermediates in intramolecular π-nucleophilic additions.

3. Experimental

All reagents were of commercial quality (Aldrich, Fluka, SDS, Probus) and were used as received. Solvents (SDS, Scharlau) were dried and purified using standard techniques. Reactions were monitored by thin layer chromatography on aluminium plates coated with silica gel or aluminium oxide with fluorescent indicator (Merck 60 F_{254}). Separations by flash chromatography were performed on silica gel (Merck 60, 230–400 mesh) or aluminium oxide (Merck 90, 70–230 mesh). Melting points were measured in open capillary tubes using a Büchi immersion apparatus or on a Reichert 723 hot stage microscope, and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrophotometer, with solid compounds compressed into KBr pellets. NMR spectra were obtained at 250 or 300 MHz for ^{1}H and at 63 or 75 MHz for ^{13}C NMR (Servicio de Espectroscopía, Universidad Complutense). When necessary, assignments were aided by DEPT, COSY, CH COLOC and ^{13}C–^{1}H correlation experiments. Elemental analyses were determined by the Servicio de Microanálisis, Universidad Complutense on a Leco 932 microanalyzer. Optical rotations were measured at 25°C on a 1 mL cell in $CHCl_3$ or MeOH at 589 nm, using a Perkin Elmer 240 polarimeter; concentrations are given in g/100 mL. HPLC analyses were performed using a Constametric 4100 system equipped with a chiral column (Chiracel OD) and UV–vis detector. Mobile phase: hexane/2-propanol (9:1).

3.1. (−)-(4*S*)-4-Methyl-1-methylene-2-phenethyl-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazoline-3,6-dione 4c

To a cold (−15°C), magnetically stirred anhydrous trifluoroacetic acid (13 mmol), bis(dimethylamino)methane (2.6 mmol) was added slowly and diluted with dry CH_2Cl_2 (10 mL). The temperature of the resulting solution was kept below −10°C and a solution of compound **1c** (2.6 mmol) in dry CH_2Cl_2 (10 mL) was then added. The cooling bath was removed and the solution was heated at 65°C for 3.5 h. To the cooled solution, H_2O (15 mL) was added and the separated aqueous layer was extracted with CH_2Cl_2, the combined organic layers were washed with water, dried over Na_2SO_4, filtered and evaporated. Chromatography of the residue in alumina (EtOAc/hexane, 1:1) provided methylene compound **4c**, together with **6c**. **4c**: white solid; yield: 77% [found: C, 73.00; H, 5.65; N, 12.34. $C_{21}H_{19}N_3O_2$ requires: C, 73.03; H, 5.54; N, 12.16%]; mp 93–95°C; $[\alpha]_D^{25} = -79$ (*c* 0.12, $CHCl_3$); ν_{max} (KBr) 1684, 1619 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.26 (dd, 1H, J = 7.9 and 1.5 Hz), 7.77 (ddd, 1H, J = 8.2, 7.5 and 1.5 Hz), 7.70 (dd, 1H, J = 8.2 and 1.5 Hz), 7.48 (ddd, 1H, J = 7.9, 7.5 and 1.5 Hz), 7.31–7.16 (m, 5H), 6.24 (d, 1H, J = 1.7 Hz), 5.50 (q, 1H, J = 7.0 Hz), 5.14 (d, 1H, J = 1.7 Hz), 4.06 (m, 2H), 2.94 (m, 2H), 1.53 (d, 3H, J = 7.0 Hz); δ_C (63 MHz, $CDCl_3$) 165.6, 159.9, 147.5, 144.8, 137.9, 136.9, 134.9, 128.9, 128.8, 127.9, 127.5, 126.9, 126.7, 120.5, 103.4, 51.5, 45.8, 32.5, 19.1.

3.2. (−)-(1*S*,4*S*)-4-Methyl-1-dimethylaminomethyl-2-phenethyl-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazoline-3,6-dione 6c

Compound **6c** was obtained as a yellow solid (alumina, EtOAc/hexane, 1:1); yield: 23% [found: C, 70.34; H, 6.58; N, 14.28. $C_{23}H_{26}N_4O_2$ requires: C, 70.75; H, 6.71; N, 14.35%]; mp 45–46°C; $[\alpha]_D^{25}=-130$ (*c* 0.12, $CHCl_3$); ν_{max} (KBr) 2933, 1685, 1586 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.28 (dd, 1H, $J=8.0$ and 1.5 Hz), 7.77 (ddd, 1H, $J=8.2$, 7.4 and 1.5 Hz), 7.69 (d, 1H, $J=8.2$ Hz), 7.50 (ddd, 1H, $J=8.0$, 7.4 and 1.4 Hz), 7.23–7.11 (m, 5H), 5.92 (dd, 1H, $J=8.0$ and 4.2 Hz), 5.50 (q, 1H, $J=7.1$ Hz), 4.1 (m, 1H), 3.90 (m, 1H), 3.82 (dd, 1H, $J=16.5$ and 4.2 Hz), 3.52 (dd, 1H, $J=16.5$ and 8.0 Hz), 3.0 (m, 2H), 2.27 (s, 6H), 1.50 (d, 3H, $J=7.1$ Hz); δ_C (63 MHz, $CDCl_3$) 166.3, 159.8, 147.1, 144.9, 137.9, 134.7, 128.9, 128.7, 127.8, 127.7, 126.9, 126.8, 124.8, 120.4, 57.7, 51.7, 46.7, 45.7, 45.6, 33.3, 17.8.

3.3. (−)-(4*S*)-4-Methyl-2-phenethyl-2,4-dihydropyrazino-[2,1-*b*]quinazoline-1,3,6-trione 10c

A mixture of **1c** (300 mg, 0.89 mmol) and PCC (388 mg, 1.8 mmol) in dry CH_2Cl_2 (15 mL) was stirred under nitrogen at room temperature overnight. After evaporation of the solvent in vacuo, the crude was chromatographed in silica gel (EtOAc/hexane, 1:1) yielding a white solid (69%) [found: C, 70.08; H, 4.71; N, 12.23. $C_{20}H_{17}N_3O_3$ requires: C, 69.15; H, 4.93; N, 12.09%]; mp 66–68°C; $[\alpha]_D^{25}=-0.5$ (*c* 0.25, $CHCl_3$); ν_{max} (KBr) 1741, 1686 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.22 (dd, 1H, $J=8.0$ and 1.4 Hz), 7.94 (d, 1H, $J=8.1$ Hz), 7.81 (ddd, 1H, $J=8.1$, 7.5 and 1.4 Hz), 7.58 (ddd, 1H, $J=8.0$, 7.5 and 0.9 Hz), 7.26–7.11 (m, 5H), 5.44 (q, 1H, $J=6.9$ Hz), 4.3 (m, 1H), 4.06 (m, 1H), 2.96 (t, 2H, $J=7.4$ Hz), 1.49 (d, 3H, $J=6.9$ Hz); δ_C (63 MHz, $CDCl_3$) 168.4, 159.3, 156.9, 146.4, 138.6, 137.3, 135.4, 129.8, 129.7, 129.2, 128.7, 127.0, 126.8, 121.7, 52.6, 42.3, 33.5, 20.9.

3.4. *N*-Methyl-4-oxo-3*H*-quinazoline-2-carboxamide 11a

Selenium oxide (505 mg, 4.55 mmol) was added to a stirred suspension of **1a** (300 mg, 1.3 mmol) in acetic anhydride (0.25 mL). The reaction mixture was stirred at 145°C overnight, filtered and the filtrate washed with acetic acid and ethyl acetate. The combined organic extracts were neutralised with NaOH 20%, dried over Na_2SO_4 and concentrated to dryness. Column chromatography (silica gel, EtOAc/hexane, 4:1) of the residue yielded **11a** as a white solid (30%); [found: C, 58.68; H, 4.63; N, 20.00. $C_{10}H_9N_3O_2$ requires: C, 59.1; H, 4.46; N, 20.67%]; mp 177–79°C; ν_{max} (KBr) 3348, 2930, 1622 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.99 (d, 1H, $J=4.6$ Hz), 8.15 (dd, 1H, $J=7.9$ and 1.4 Hz), 7.87 (dd, 1H, $J=7.5$ and 1.4 Hz), 7.75 (d, 1H, $J=7.6$ Hz), 7.54 (ddd, 1H, $J=7.9$, 7.5 and 1 Hz), 2.81 (d, 3H, $J=4.6$ Hz). δ_C (63 MHz, $CDCl_3$) 159.8, 159.7, 145.7, 134.9, 134.7, 134.6, 127.9, 126.1, 115.2, 26.2.

3.5. Addition of RM. Preparation of 1-hydroxy-1-alkyl-(aryl)-pirazino[2,1-*b*]quinalzolinones. General procedure

To a solution of **9** (0.39 mmol) in dry THF (7 mL) was added, under nitrogen, a solution of RLi (0.5 mmol) at −30°C or a solution of RMgBr (0.5 mmol) at −78°C. The resulting mixture was stirred for 3 h, quenched by the addition of a saturated solution of amonium chloride (1 mL), and allowed to warm to 20°C. Ethyl acetate was added (10 mL), the organic layer was separated and the aqueous phase was extracted with EtOAc (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (silica gel) afforded pure products.

3.6. (−)-(1*R*,4*S*)-1-Hydroxy-2,4-dimethyl-1-phenyl-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazoline-3,6-dione 12

Compound **12** was obtained (EtOAc/hexane, 2:3) as a white solid; yield: 95% [found: C, 67.83; H, 5.13; N, 12.75. $C_{19}H_{17}N_3O_3$ requires: C, 68.05; H, 5.11; N, 12.52%]; mp 68–69°C; $[\alpha]_D^{25}=-18$ (*c* 0.19, $CHCl_3$); ν_{max} (KBr) 3380, 1669, 1607 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.20 (d, 1H, $J=8.2$ Hz), 7.80–7.77 (m, 2H), 7.54–7.32 (m, 6H), 6.35 (s, 1H), 5.30 (q, 1H, $J=7.2$ Hz), 3.26 (s, 3H), 1.34 (d, 3H, $J=7.2$ Hz). δ_C (63 MHz, $CDCl_3$) 167.4, 159.9, 152.6, 145.9, 140.4, 135.2, 129.6, 128.4, 127.9, 127.2, 126.6, 126.4, 120.7, 84.5, 53.2, 28.9, 17.6.

3.7. (−)-(1*R*,4*S*)-1-Hydroxy-1,2,4-trimethyl-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazoline-3,6-dione 13

Compound **13** was obtained (EtOAc/hexane, 4:1) as a white solid; yield: 73% [found: C, 61.75; H, 5.55; N, 15.14. $C_{14}H_{15}N_3O_3$ requires: C, 61.52; H, 5.53; N, 15.37%]; mp 167–168°C; $[\alpha]_D^{25}=-46$ (*c* 0.12 $CHCl_3$); ν_{max} (KBr) 3157, 1693, 1655, 1609 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.24 (dd, 1H, $J=8.0$ and 1.5 Hz), 7.77 (ddd 1H, $J=8.0$, 7.5 and 1.5 Hz), 7.66 (d, 1H, $J=8.0$ Hz), 7.50 (ddd, 1H, $J=8.0$, 7.5 and 1.2 Hz), 5.29 (s, 1H), 5.26 (q, 1H, $J=7.1$ Hz), 3.13 (s, 3H), 1.78 (s, 3H), 1.69 (d, 3H, $J=7.1$ Hz). δ_C (63 MHz, $CDCl_3$) 165.6, 159.7, 153.3, 145.9, 134.9, 127.6, 126.8, 126.7, 120.5, 82.3, 52.4, 29.2, 26.8, 18.4.

3.8. (+)-(1*R*,4*S*)-1-Benzyl-1-hydroxy-2,4-dimethyl-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazoline-3,6-dione 14

Compound **14** was obtained ($CHCl_3$/EtOAc, 2:1) as a white solid; yield: 73% [found: C, 68.43; H, 5.50; N, 12.10. $C_{20}H_{19}N_3O_3$ requires: C, 68.75; H, 5.48; N, 12.03%]; mp 48–49°C; $[\alpha]_D^{25}=+90$ (*c* 0.2, $CHCl_3$); ν_{max} (KBr) 3326, 1684, 1594 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.19 (dd, 1H, $J=7.9$ and 1.5 Hz), 7.8 (ddd, 1H, $J=8.2$, 7.5 and 1.5 Hz), 7.72 (dd, 1H, $J=8.2$ and 1.3 Hz), 7.5 (ddd, 1H, $J=7.9$, 7.5 and 1.3 Hz), 7.15 (m, 1H), 7.06 (dt, 2H, $J=7.4$ and 1.5 Hz), 6.62 (dd, 2H, $J=7.6$ and 1.4 Hz), 5.02 (s, 1H), 4.06 (q, 1H, $J=6.7$ Hz), 3.50 (d, 1H, $J=13.5$ Hz), 3.39 (d, 1H, $J=13.5$ Hz), 3.28 (s, 3H), 1.48 (d, 3H, $J=6.7$ Hz). δ_C (63 MHz, $CDCl_3$) 166.9, 159.8, 151.5, 146.1 135.0, 133.2, 129.3, 128.8, 128.1, 127.7, 127.1, 127.0, 120.8, 86.7, 52.2, 48.1, 28.3, 20.2.

3.9. (+)-(1*R*,4*S*)-1-Hydroxy-1,4-dimethyl-2-phenethyl-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazoline-3,6-dione 18

Compound **18** was obtained (EtOAc/hexane, 2:3) as a white solid; yield: 56% [found: C, 69.51; H, 5.77; N, 11.65. $C_{21}H_{21}N_3O_3$ requires: C, 69.40; H, 5.82; N, 11.56%]; mp 108–109°C; $[\alpha]_D^{25}=+43$ (*c* 0.13, $CHCl_3$); ν_{max} (KBr) 3398, 1689, 1668 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.28 (dd, 1H, $J=7.9$ and 1.5 Hz), 7.80 (ddd, 1H, $J=8.1$, 7.6 and 1.5 Hz), 7.69 (dd, 1H, $J=8.1$ and 1.2 Hz), 7.53 (ddd, 1H, $J=7.9$, 7.6 and 1.2 Hz), 7.28–7.15 (m, 5H), 5.31 (q, 1H, $J=7.1$ Hz), 5.23 (s, 1H), 4.04 (m, 1H), 3.56 (m, 1H), 2.93 (m, 2H), 1.76 (s, 3H), 1.74 (d, 3H, $J=7.1$ Hz); δ_C (63 MHz, $CDCl_3$) 165.4, 160.0, 153.5, 146.1, 139.1, 135.0, 128.9, 128.4, 127.7, 127.0, 126.4, 120.6, 82.7, 52.7, 43.6, 35.7, 30.6, 18.3.

3.10. (−)-(1*R*,4*S*)-1-Hydroxy-4-methyl-2-phenethyl-1-phenyl-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazoline-3,6-dione 19

Compound **19** was obtained (EtOAc/hexane, 1:2) as a white solid; yield: 97% [found: C, 73.52; H, 5.37; N, 9.62. $C_{26}H_{23}N_3O_3$ requires: C, 73.39; H, 5.45; N, 9.87%]; mp 76–78°C; $[\alpha]_D^{25}=-64$ (*c* 0.13, $CHCl_3$); ν_{max} (KBr) 3413, 1690, 1669 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.25 (d, 1H, $J=7.8$ Hz), 7.82–7.78 (m, 2H), 7.52 (m, 1H), 7.41–7.28 (m, 5H), 7.24–7.11 (m, 5H), 6.28 (s, 1H), 5.34 (q, 1H, $J=7.2$ Hz), 4.35 (m, 1H), 3.6 (m, 1H), 2.9 (m, 2H), 1.28 (d, 3H, $J=7.2$ Hz); δ_C (63 MHz, $CDCl_3$) 167.1, 159.8, 152.5, 145.7, 140.8, 138.9, 134.9, 129.4, 128.9, 128.3, 127.8, 127.1, 126.9, 126.3, 126.2, 120.6, 85.0, 53.1, 45.4, 35.8, 17.3.

3.11. (+)-(1*R*,4*S*)- and (−)-(1*S*,4*S*)-1-Methoxy-2,4-dimethyl-1-phenyl-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]-quinazoline-3,6-dione 15 and 16

A mixture of **12** (280 mg, 0.84 mmol) and *p*-toluenesulfonic acid (catalytic amount) in methanol (20 mL) was refluxed for 2 h. The mixture was cooled, concentrated in vacuo and the residue partitioned between CH_2Cl_2 and a saturated sodium bicarbonate solution. The organic layer was dried over Na_2SO_4 and concentrated to dryness. The residue was subjected to column chromatography (alumina, Et_2O) yielding **15** (54%) and **16** (7%).

15: [Found: C, 68.32; H, 5.39; N, 12.25. $C_{20}H_{19}N_3O_3$ requires: C, 68.75; H, 5.48; N, 12.03%.] mp 141–142°C; $[\alpha]_D^{25}=+112$ (*c* 0.14, $CHCl_3$); ν_{max} (KBr) 1670, 1592 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.21 (dd, 1H, $J=7.9$ and 0.9 Hz), 7.76–7.72 (m, 2H), 7.66–7.61 (m, 2H), 7.46 (m, 1H), 7.42–7.28 (m, 3H), 5.43 (q, 1H, $J=7.0$ Hz), 3.25 (s, 3H), 2.98 (s, 3H), 1.67 (d, 3H, $J=7.0$ Hz). δ_C (63 MHz, $CDCl_3$) 168.3, 160.2, 148.8, 147.2, 138.7, 134.9, 129.5, 128.7, 128.1, 127.7, 127.0, 126.7, 120.4, 92.3, 52.0, 51.4, 20.0, 14.3.

16: white solid: [Found: C, 68.41; H, 5.02; N, 11.95. $C_{20}H_{19}N_3O_3$ requires: C, 68.75; H, 5.48; N, 12.03%.] mp 164–166°C; $[\alpha]_D^{25}=-59$ (*c* 0.09, $CHCl_3$); ν_{max} (KBr) 1684, 1590 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.23 (dd, 1H, $J=8.0$ and 1.5 Hz), 7.68 (ddd, 1H, $J=7.9$, 7.6 and 1.5 Hz), 7.56 (dd, 1H, $J=7.9$ and 1.3 Hz), 7.45 (ddd, 1H, $J=8.0$, 7.6 and 1.3 Hz), 7.40–7.25 (m, 5H), 5.48 (q, 1H, $J=6.8$ Hz), 3.42 (s, 3H), 2.72 (s, 3H), 1.79 (d, 3H, $J=6.8$ Hz). δ_C (63 MHz, $CDCl_3$) 168.2, 160.4, 149.2, 146.9, 140.3, 134.8, 128.2, 128.0, 127.4, 127.2, 126.1, 125.5, 120.4, 92.8, 52.0, 51.9, 29.3, 20.9.

3.12. Cyclisation reactions. Synthesis of isoquino-[1′,2′:3,4]pyrazino[2,1-*b*]quinazolinones. General procedure

A solution of (0.28 mmol) in concentrated sulfuric acid (2 mL) was stirred at room temperature overnight, then poured onto ice and the precipitate thus formed was filtered and washed with water. The solid residue was chromatographed in silica gel to afford the pure products.

3.13. (−)-(9*S*,16b*S*)-9,16b-Dimethyl-5,6,9,16b-tetrahydroisoquino[1′,2′:3,4]pyrazino[2,1-*b*]quinazoline-8-11-dione 7

Compound **7** was obtained (EtOAc/hexane, 1:2) as a white solid; yield: 75% [found: C, 72.94; H, 5.37; N, 12.08. $C_{21}H_{19}N_3O_2$ requires: C, 73.02; H, 5.54; N, 12.16%]; mp 76–78°C; $[\alpha]_D^{25}=-30$ (*c* 0.11, $CHCl_3$); ν_{max} (KBr) 1684, 1589 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.29 (dd, 1H, $J=7.8$ and 0.8 Hz), 7.82 (m, 1H), 7.79 (dd, 1H, $J=7.6$ and 1.3 Hz), 7.52 (m, 1H), 7.32 (dd, 1H, $J=7.9$ and 0.9 Hz), 7.21 (ddd, 1H, $J=7.2$, 6.2 and 0.9 Hz), 7.14 (dd, 1H, $J=7.2$ and 0.9 Hz), 7.03 (ddd, 1H, $J=7.9$, 7.2 and 0.9 Hz), 5.36 (q, 1H, $J=7.0$ Hz), 4.92 (dd, 1H, $J=14.0$ and 8.9 Hz), 3.66 (ddd, 1H, $J=14.0$, 8.9 and 6.5 Hz), 3.34 (dd, 1H, $J=17.5$ and 8.9 Hz), 2.89 (dd, 1H, $J=17.5$ and 6.5 Hz), 2.26 (s, 3H), 1.01 (d, 3H, $J=7.0$ Hz); δ_C (63 MHz, $CDCl_3$) 169.7, 160.5, 150.8, 146.8, 139.8, 134.8, 132.5, 130.6, 128.2, 128.0, 127.5, 126.8, 126.4, 124.1, 120.5, 63.3, 51.3, 37.1, 30.7, 25.9, 18.6.

3.14. (−)-(9*S*,16b*R*)-9,16b-Dimethyl-5,6,9,16b-tetrahydroisoquino[1′,2′:3,4]pyrazino[2,1-*b*]quinazoline-8-11-dione 8

Compound **8** was obtained (EtOAc/hexane, 1:2) as a white solid; yield: 19% [found: C, 73.18; H, 5.26; N, 12.32. $C_{21}H_{19}N_3O_2$ requires: C, 73.02; H, 5.54; N, 12.16%]; mp 75–77°C; $[\alpha]_D^{25}=-42$ (*c* 0.33, $CHCl_3$); ν_{max} (KBr) 1734, 1684, 1662 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.22 (d, 1H, $J=8.1$ Hz), 8.18 (d, 1H, $J=7.7$ Hz), 7.69 (dd, 1H, $J=8.1$ and 6.9 Hz), 7.59 (d, 1H, $J=8.1$ Hz), 7.44 (dd, 1H, $J=8.1$ and 6.9 Hz), 7.35 (dd, 1H, $J=7.7$ and 7.5 Hz), 7.25 (d, 1H, $J=7.5$ Hz), 7.09 (d, 1H, $J=7.5$ Hz), 5.45 (q, 1H, $J=7.1$ Hz), 5.04 (m, 1H), 2.98 (m, 2H), 2.74 (d, 1H, $J=13.0$ Hz), 2.12 (s, 3H), 1.82 (d, 3H, $J=7.1$ Hz); δ_C (63 MHz, $CDCl_3$) 167.3, 160.9, 151.8, 146.5, 135.7, 135.3, 134.4, 132.9, 128.5, 127.8, 127.5, 127.3, 126.5, 125.1, 120.0, 63.0, 52.2, 37.4, 32.3, 29.9, 18.8.

3.15. (−)-(9*S*,16b*R*)-9-Methyl-16b-phenyl-5,6,9,16b-tetrahydroisoquino[1′,2′:3,4]pyrazino[2,1-*b*]quinazoline-8-11-dione 20

Compound **20** was obtained ($CHCl_3$/EtOAc, 9:1) as a white solid; yield: 54% [found: C, 76.19; H, 4.95; N, 10.17. $C_{26}H_{21}N_3O_2$ requires: C, 76.64; H, 5.19; N, 10.31%]; mp 111–113°C; $[\alpha]_D^{25}=-236$ (*c* 0.33, $CHCl_3$); ν_{max} (KBr) 1671, 1596 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.25 (dd, 1H, $J=7.9$ and 1.5 Hz), 7.70 (ddd, 1H, $J=8.2$, 7.6 and 1.5 Hz), 7.54 (d, 1H, $J=8.2$ Hz), 7.48 (ddd, 1H, $J=7.9$, 7.5 and 1.2 Hz), 7.41 (m, 1H), 7.32–7.27 (m, 3H), 7.25–7.17 (m, 5H), 5.39 (q, 1H, $J=7.2$ Hz), 5.16 (m, 1H), 3.47 (m, 1H), 2.92 (m, 2H), 0.78 (d, 3H, $J=7.2$ Hz); δ_C (63 MHz, $CDCl_3$) 169.9, 161.0, 151.3, 146.1, 145.1, 134.8, 134.3, 133.6, 133.0, 129.1, 128.5, 128.3, 127.5, 127.3, 126.4, 126.3, 125.2, 120.3, 68.2, 53.6, 41.3, 29.9, 15.0.

3.16. (−)-(9*S*,16b*S*)-9-Methyl-16b-phenyl-5,6,9,16b-tetrahydroisoquino[1′,2′:3,4]pyrazino[2,1-*b*]quinazoline-8-11-dione 21

Compound **21** was obtained ($CHCl_3$/EtOAc, 9:1) as a white solid; yield: 34% [found: C, 76.39; H, 5.29; N, 10.19. $C_{26}H_{21}N_3O_2$ requires: C, 76.64; H, 5.19; N, 10.31%]; mp 104–105°C; $[\alpha]_D^{25}=-166$ (*c* 0.27, $CHCl_3$); ν_{max} (KBr) 1684, 1590 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.26 (dd, 1H, $J=7.6$ and 1.3 Hz), 7.68 (ddd, 1H, $J=7.9$, 7 and 1.5 Hz), 7.53–7.47 (m, 2H), 7.45 (m, 1H), 7.33 (m, 2H), 7.28–7.14 (m, 4H), 7.03–6.99 (m, 2H), 5.51 (q, 1H, $J=7.0$ Hz), 4.59 (ddd, 1H, $J=13.3$, 8.2 and 2.3 Hz), 3.24 (dd, 1H, $J=13.3$ and 9.0 Hz), 2.98 (ddd, 1H, $J=14.9$, 9 and 8.2 Hz), 2.56 (dd, 1H, $J=14.9$ and 6.5 Hz), 1.12 (d, 3H, $J=7.0$ Hz); δ_C (63 MHz, $CDCl_3$) 169.3, 160.3, 146.6, 143.8, 136.1, 134.6, 134.5, 130.6, 129.0, 128.9, 128.2, 128.1, 128.0, 127.7, 127.4, 126.6, 126.5, 126.1, 120.0, 70.2, 51.4, 38.5, 26.2, 18.8.

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References

1. Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds. Additions to *N*-acyliminium ions; Pergamon Press: Oxford, 1991; Vol. 2, pp. 1047–1082.
2. Heaney, H.; Shuhaibar, K. F. *Synlett* **1995**, 47–48.
3. Lögers, M.; Overman, L. E.; Welmaker, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 9139–9150.
4. Rigo, B.; El Ghammarti, S.; Couturier, D. *Tetrahedron Lett.* **1996**, *37*, 485–486.
5. Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *Tetrahedron Lett.* **1998**, *39*, 4905–4908.
6. Wang, H.; Ganesan, A. *Org. Lett.* **1999**, *1*, 1647–1649.
7. Pen, J.; Mantle, P. G.; Bilton, J. N.; Sheppard, R. N. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1495–1496.
8. Takahashi, C.; Matsushita, T.; Doi, M.; Minoura, K.; Shingu, T.; Kumeda, Y.; Numatta, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2345–2353.
9. Fujimoto, H.; Negishi, E.; Yamaguchi, K.; Nishi, N.; Yamazaki, M. *Chem. Pharm. Bull.* **1996**, *44*, 1843–1848.
10. Hochlowski, J. E.; Mullally, M. M.; Spanton, S. G.; Whittern, D. N.; Hill, P.; McAlpine, J. B. *J. Antibiot.* **1993**, *46*, 380–386.
11. Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953–11963.
12. Martín-Santamaría, S.; Espada, M.; Avendaño, C. *Tetrahedron* **1999**, *55*, 1755–1762.
13. Sánchez, J. D.; Ramos, M. T.; Avendaño, C. *Tetrahedron Lett.* **2000**, *41*, 2745–2748.
14. Sánchez, J. D.; Ramos, M. T.; Avendaño, C. *J. Org. Chem.* **2001**, *66*, 5731–5735.
15. Fernández, M.; Heredia, M. L.; de la Cuesta, E.; Avendaño, C. *Tetrahedron: Asymmetry* **2001**, *12*, 411–418.
16. Ottenheijm, H. C. J.; Plate, R.; Noordik, J. H.; Herscheid, J. D. M. *J. Org. Chem.* **1982**, *47*, 2147–2154.
17. Fernández, M.; Heredia, M. L.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **1998**, *54*, 2777–2784.
18. Lee, Y. S.; Kang, D. W.; Lee, S. J.; Park, H. *J. Org. Chem.* **1995**, *60*, 7149–7152.
19. Collado, M. I.; Manteca, I.; Sotomayor, N.; Villa, M.-J.; Lete, E. *J. Org. Chem.* **1997**, *62*, 2080–2092.
20. Buenadicha, F. L.; Bartolomé, M. T.; Aguirre, M. J.; Avendaño, C.; Söllhuber, M. *Tetrahedron: Asymmetry* **1998**, *9*, 483–501.
21. Evans, W. C.; Ridgion, J. M.; Simonsen, J. L. *J. Chem. Soc.* **1934**, 137–141.
22. Helmchen, G.; Selim, A.; Dorsch, D.; Taufer, I. *Tetrahedron Lett.* **1983**, *24*, 3213–3216.
23. Heredia, M. L.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **2001**, *57*, 1987–1994.