Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 4275–4284

TETRAHEDRON: *ASYMMETRY*

Asymmetrically induced alkylation of 2-benzyl-4-isopropyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione

Félix L. Buenadicha, Carmen Avendaño * and Mónica Söllhuber

Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad Complutense, 28040 Madrid, Spain

Received 6 November 1998; accepted 11 November 1998

Abstract

The substitution of the 4-methyl group by a 4-isopropyl group in the 2-benzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione system allows a notable improvement in the stereoselective alkylation at C-1. The configuration of the newly introduced stereogenic centre has been assigned on the basis of ^{1}H NMR data and NOE measurements. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

By far the most popular and extensively studied glycine template among Schöllkopf's bis-lactim ethers used as anion precursors in the synthesis of optically active α-amino acids, is that derived from valine and glycine.[1] Its homologue derived from *cyclo*-Val-Ala has also been used for similar purposes.[2]

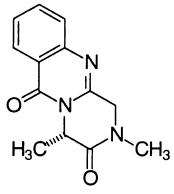
Anions derived from *N*,*N*′-disubstituted chiral piperazine-2,5-diones have been exploited to a much lesser extent than the bis-lactim ethers. Intramolecular C–C bond-forming cyclizations,[3] asymmetric induction studies[4] and enhancement of diastereocontrol by chiral relay auxiliary[5] have been reported in this context.

We have shown that, because of its locked pseudoaxial disposition, the 4-methyl substituent in anions derived from 2-substituted (4*S*)-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones (**1a** and **1b**) induces the asymmetric alkylation at C-1, with the preferential formation of the 1,4-*anti* isomers in kinetically controlled reactions. Under thermodynamic conditions, these isomers equilibrate to the more stable *syn*-isomers through the corresponding anions.[6,7] This tricyclic system can be considered a β-turn template and attracted our attention because it contains three of the six rings of the fungal metabolite *N*-acetylardeemin. This natural compound has been described as a potent reversal agent of multiple drug resistance (MDR) in tumour cell lines[8] by inhibiting the membrane glycoprotein Pgp-170, which is thought to function by lowering the intracellular levels of many antineoplastic drugs.[9] In our

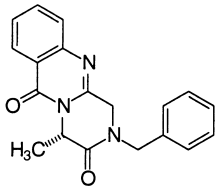
* Corresponding author. E-mail: msollhub@eucmax.sim.ucm.es

PII: S0957-4166(98)00464-9

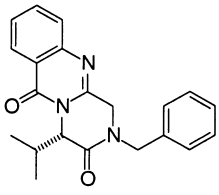
current work, aiming at the synthesis of analogues for structure–activity relationships, we have found that some simple analogues, especially the C-1 alkylated derivatives of **1b**, retain most of the biological activity of *N*-acetylardeemin.[10] Here we study, from a stereochemical point of view, the alkylation of compound **2** derived from L-Val, Gly and anthranilic acid, expecting that the bulkier substituent at C-4 would induce the asymmetric alkylation at C-1 with better d.e. than those described for compound **1b**.



1a



1b



2

2. Results and discussion

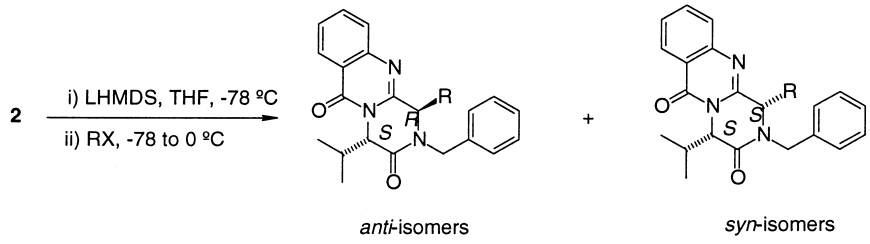
Compound **2** was prepared[11] starting from ethyl *N*-benzylglycinate and Cbz-(L)-valine, cyclization of the dipeptide to the piperazinedione, conversion to the corresponding iminoether and condensation with anthranilic acid. The results obtained by treatment of **2** with LHMDS at −78°C, followed by addition of 1.1 equivalents of the alkylating agent to give compounds **3**–**10**, are summarized in Table 1. For comparison purposes, the *anti/syn* ratios previously found in the same reactions on compound **1b**[6] have been included in brackets. In the case of the 1-arylmethyl derivatives, both diastereomers could be clearly distinguished by ^{1}H NMR assignment. Similarly to the 1-alkyl derivatives of compound **1b**, the *anti*-isomers of compounds **5**–**10** show a upfield shift for H-4 of about 1 ppm (δ=5.4 to δ=4.4 ppm) with respect to the *syn*-isomers. These data suggest that the piperazine ring adopts a boat conformation in the *syn*-isomers, while this ring is more planar in the *anti*-isomers. The assignment in the case of **3** and **4**, where both isomers present the same chemical shift for H-4 ($\delta\approx$5.4 ppm), required NOE experiments, which also corroborated the structure of isomers **5**–**9**: see, for instance, the most significant NOEs for both isomers of compound **5** in Fig. 1. The enantiomeric purity was determined by ^{1}H NMR (addition of europium(III) tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] [(+)-Eu(HFC)$_3$] as chiral shift reagent).

The reactions with compound **2** are more diastereoselective than with compound **1b**, as would be expected from the greater steric interaction of the C-4 isopropyl substituent. In addition, ratios higher than 8:2 in favour of the *anti*-isomers were found for compounds **5**–**9**. Also noteworthy is the appearance of significant amounts of the *anti*-isomer of compound **3** (since this isomer was not isolated when compounds **1a** or **1b** were alkylated with methyl iodide), and the significant improvement of the diastereoselection found in the alkylation of **2** with *p*-nitrobenzyl bromide.

According to the proposed mechanism, the reverse diastereoselectivity found with the earlier-mentioned electrophiles and the anion derived from **1a** and **1b** (0:100 for **1** and 30:70 for **2**) was explained on the basis of the faster equilibration by epimerization at C-1 as a result of either a more favourable alignment of H-1 for deprotonation in the 1-methyl derivatives, or the greater acidity of this proton in the *p*-nitrobenzyl derivatives with respect to the C-1 arylmethyl substituted compounds.

The lower d.e. observed in these reactions in comparison with the d.e. described for derivatives of *cyclo*-Val-Gly bis-lactim ethers[1] can be explained by the easier equilibration of the kinetically favoured *anti*-isomers to the more stable *syn*-isomers in compounds **3**–**9**.

Table 1
1-Alkylated derivatives of **2**



Compound	R-X	*anti* (Yield %)	*syn* (Yield %)	*anti/syn*[a] ( )[b]
3	CH_3I	27	60	31/69 (0/100)
4	CH_2=CH-CH_2Br	38[c]	15[c]	72/28 (63/37)
5	$C_6H_5CH_2Br$	50[c]	5[c]	91/9 (74/26)
6	*p*-CH_3-$C_6H_4CH_2Br$	53	6	88/12 (66/33)
7	*p*-NO_2-$C_6H_4CH_2Br$	66	8	89/11 (30/70)
8	*m*-Cl-$C_6H_4CH_2Br$	55	12	82/18 (54/46)
9	2-naphthylmethylBr	40	9	82/18 (60/40)

[a]e.e. > 95% for all compounds was shown. [b]*Anti/syn* relationship found with **1b** as template. [c]Appreciable amounts of the 1,1-dialkylated products (see compounds **10**, **11** in Experimental) were also obtained.

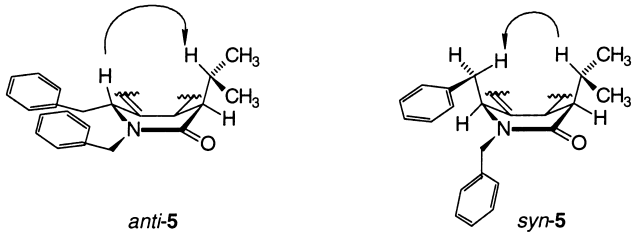
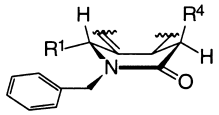


Figure 1. Significant NOEs observed in *anti*- and *syn*-diastereomers of compound **5**

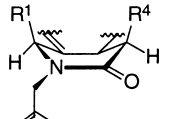
A high-temperature molecular dynamics study of representative compounds derived from **1b** and **2** was carried out using the HyperChem 3 program in order to explore their putative minimum energy conformations. To avoid the risks inherent to this methodology, additional molecular dynamics was used and, finally, the minimum energy conformers were minimized using MM calculations and the Fletcher–Reeves algorithm (RMS gradient 0.01 kcal/Å mol) (Table 2).

It can be seen from Table 2 that the *anti*-isomers are less stable than the *syn*-isomers in all cases, and

Table 2
Calculated energies (MM2, kcal/mol) for some representative compounds



anti-isomers



syn-isomers

R^1	R^4	calcd. energies for the *anti*-isomers	calcd. energies for the *syn*-isomers
Me	Me	2.27	0.80
Me	*i*-Pr	2.23	1.13
Bn	Me	3.12	0.92
Bn	*i*-Pr	3.26	1.76

that the calculated energy differences are greater in derivatives with a C-4 methyl substituent. According to the more planar conformation for the piperazine ring, the replacement of the methyl group at C-4 by an isopropyl group does not affect the minimum energy in the *anti*-isomers, but in the *syn*-isomers the boat conformation presents a greater 1,4-steric interaction in the isopropyl derivatives, which could explain the higher diastereoselectivity in the asymmetrically induced alkylation at C-1.

3. Experimental

3.1. General methods

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, 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 Servicio de Microanálisis, U.C.M. Optical rotations were determined at 25°C in $CHCl_3$ 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.

3.2. (4S)-2-Benzyl-4-isopropyl-2,4-dihydro-1H-pyrazino[2,1-b]quinazoline-3,6-dione ***2***

To a stirred solution of 4.35 g (22.4 mmol) of distilled ethyl *N*-benzylglycinate in 80 ml dry CH_2Cl_2, *N*-Cbz-(L)-valine (5.65 g, 22.4 mmol) and DCC (5.1 g 24.6 mmol) were added, and stirring was continued overnight. The reaction mixture was filtered, washed successively with HCl (1N), $NaHCO_3$ (1N) and water, dried over anhydrous Na_2SO_4 and evaporated. The syrupy residue (8.9 g, 20.1 mmol; yield 93%) was hydrogenated at 35 psi for 14 h with 0.8 g of C/Pd (10%) in 150 ml of methanol, filtered (Celite), and evaporated. The obtained syrup was recrystallized from toluene to give 4.76 g (98%) of (3*S*)-3-isopropyl-1-benzylpiperazine-2,5-dione. Mp: 137–138°C. $[\alpha]_D$ +2.15 (0.25, chloroform). IR (KBr) ν: 3329, 1684, 1641 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.29 (5H, m-ArH), 6.25 (1H, s, NH), 4.74 (1H, d, *J*=14.3 Hz, Ar–CH_2–N), 4.43 (1H, d, *J*=14.3 Hz, Ar–CH_2–N), 3.90 (1H, m, H-3), 3.86 (1H, d, *J*=17.7 Hz, H-6), 3.76 (1H, d, *J*=17.7 Hz, H-6), 2.44 (1H, sep, *J*=6.8 Hz, *CH*(CH_3)$_2$), 1.01 (3H, d, *J*=6.8 Hz, CH_3), 0.86

(3H, d, *J*=6.8 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 166.5, 166.5, 135.1, 128.8, 128.5, 128.1, 60.6, 49.5, 48.5, 33.1, 18.8, 16.1. Analysis calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.34; H, 7.39; N, 11.48.

A mixture of 2 g (8.1 mmol) of the earlier-described (3*S*)-1-benzyl-3-isopropylpiperazine-2,5-dione, triethyloxonium tetrafluoroborate (4.6 g, 24.2 mmol) and anhydrous Na_2CO_3 (4.27 g, 40.3 mmol) in 75 ml dry CH_2Cl_2 was stirred overnight at room temperature, poured on ice water, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4 and evaporated. Anthranilic acid (1.48 g, 10.8 mmol) was added to the syrupy residue, the mixture was stirred vigorously at 120°C for 3 h under argon, dissolved in CH_2Cl_2, extracted with diluted ammonium hydroxide, dried (Na_2SO_4) and concentrated. Column chromatography (CH_2Cl_2:EtOAc 9:1) afforded 1.35 g (48%) of **2** as a syrup. $[\alpha]_D$ +35.0 (0.25, chloroform). IR (KBr) ν: 1676, 1607 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.23 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.71 (1H, ddd, *J*=8.4, 7.2, 1.5 Hz, H-9), 7.54 (1H, dd, *J*=8.4, 1.1 Hz, H-10), 7.45 (1H, ddd, *J*=8.0, 7.2, 1.1 Hz, H-8), 7.32 (5H, m, ArH), 5.25 (1H, d, *J*=7.8 Hz, H-4), 4.95 (1H, d, *J*=14.5 Hz, Ar–CH_2–N), 4.49 (1H, d, *J*=17.2 Hz, H-1), 4.31 (1H, d, *J*=14.5 Hz, Ar–CH_2–N), 4.21 (1H, d, *J*=17.2 Hz, H-1), 2.14 (1H, m, $CH(CH_3)_2$), 0.99 (3H, d, *J*=7.2 Hz, CH_3), 0.99 (3H, d, *J*=7.2 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 165.5, 160.3, 148.4, 146.9, 135.3, 134.5, 128.9, 128.3, 128.1, 126.93, 126.90, 126.7, 120.2, 60.7, 49.7, 49.5, 31.9, 19.8, 18.7. Analysis calcd for $C_{21}H_{21}N_3O_2$: C, 72,60; H, 6.09; N, 12.10. Found: C, 72.41; H, 6.32; N, 11.45.

*3.3. General procedure for the alkylation of compound **2***

To a cold (−78°C), magnetically stirred solution of compound **2** (0.5 mmol) in dry THF (10 ml) was added, under argon, dropwise via syringe, a 1 M solution of lithium hexamethyldisilazide in THF (0.7 ml), followed by the appropriate halide (0.7 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 10–30 min, quenched with ice, and diluted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. Column chromatography of the residue on silica gel (toluene:ethyl acetate, 9:1 if not otherwise indicated) afforded first the 1,1-dialkylated product, if any, followed by the *anti*-1-alkylated and the *syn*-alkylated compounds. In some cases traces of the 1-hydroxy derivative of **2** were isolated. Yields are included in Table 1; analytical and spectroscopic data follow.

*3.4. (1*R,*4*S*)-2-Benzyl-4-isopropyl-1-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione* anti-***3***

Yellow oil (petroleum ether:ethyl acetate 1:1). $[\alpha]_D$ +15.3 (0.25, chloroform). IR (NaCl) ν: 1678, 1604 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.27 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.74 (1H, ddd, *J*=8.3, 7.0, 1.5 Hz, H-9), 7.64 (1H, dd, *J*=8.3, 1.2 Hz, H-10), 7.48 (1H, ddd, *J*=8.0, 7.0, 1.2 Hz, H-8), 7.30 (5H, m, ArH), 5.43 (1H, d, *J*=8.9 Hz, H-4), 5.39 (1H, d, *J*=15.7 Hz, Ar–CH_2–N), 4.77 (1H, q, *J*=6.8 Hz, H-1), 4.31 (1H, d, *J*=15.7 Hz, Ar–CH_2–N), 2.26 (1H, m, *CH*$(CH_3)_2$), 1.74 (3H, d, *J*=6.8 Hz, CH_3), 1.21 (3H, d, *J*=6.8 Hz, CH_3), 1.02 (3H, d, *J*=6.8 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 167.4, 160.8, 151.7, 146.9, 137.0, 134.5, 128.8, 127.5, 127.4, 127.1, 127.0, 126.9, 120.3, 60.7, 52.9, 45.3, 31.0, 19.8, 19.3, 16.0. Analysis calcd for $C_{22}H_{23}N_3O_2$: C, 73.11; H, 6.41; N, 11.63. Found: C, 72.69; H, 6.52; N, 11.32.

3.5. (1S,4S)-2-Benzyl-4-isopropyl-1-methyl-2,4-dihydro-1H-pyrazino[2,1-b]quinazoline-3,6-dione syn-**3**

Yellow oil (petroleum ether:ethyl acetate 1:1). $[\alpha]_D$ −0.8 (0.25, chloroform). IR (NaCl) ν: 1680, 1603 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.24 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.72 (1H, ddd, *J*=8.4, 7.1, 1.5 Hz, H-9), 7.53 (1H, dd, *J*=8.4, 1.1 Hz, H-10), 7.44 (1H, ddd, *J*=8.0, 7.1, 1.1 Hz, H-8), 7.27 (5H, m, ArH), 5.31 (1H, d, *J*=8.8 Hz, H-4), 5.22 (1H, d, *J*=14.8 Hz, Ar–CH_2–N), 4.56 (1H, q, *J*=7.2 Hz, H-1), 4.22 (1H, d, *J*=14.8 Hz, Ar–CH_2–N), 2.16 (1H, m, *CH*(CH_3)$_2$), 1.68 (3H, d, *J*=7.2 Hz, CH_3), 1.27 (3H, d, *J*=6.8 Hz, CH_3), 0.99 (3H, d, *J*=6.8 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 165.8, 161.0, 152.1, 147.0, 135.7, 134.6, 128.9, 128.3, 128.0, 127.1, 126.9, 126.6, 119.9, 60.0, 55.9, 47.5, 34.0, 20.5, 20.4, 19.4. Analysis calcd for $C_{22}H_{23}N_3O_2$: C, 73.11; H, 6.41; N, 11.63. Found: C, 72.87; H, 6.53; N, 11.23.

3.6. (1R,4S)-1-Allyl-2-benzyl-4-isopropyl-2,4-dihydro-1H-pyrazino[2,1-b]quinazoline-3,6-dione anti-**4**

Oil (petroleum ether:ethyl acetate 6:4). $[\alpha]_D$ +44.4 (0.25, chloroform). IR (NaCl) ν: 1679, 1601 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.24 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.72 (1H, ddd, *J*=8.3, 7.2, 1.5 Hz, H-9), 7.58 (1H, dd, *J*=8.3, 1.1 Hz, H-10), 7.46 (1H, ddd, *J*=8.0, 7.2, 1.1 Hz, H-8), 7.33 (5H, m, ArH), 5.64 (1H, d, *J*=15.1 Hz, Ar–CH_2–N), 5.55 (1H, ddt, *J*=13.7, 9.6, 6.8 Hz, H-2′′), 5.31 (1H, d, *J*=5.1 Hz, H-4), 5.07 (1H, dd, *J*=9.63, 1.3 Hz, H-3′′), 5.04 (1H, dd, *J*=13.7, 1.3 Hz, H-3′′), 4.65 (1H, dd, *J*=4.3, 3.3 Hz, H-1), 4.09 (1H, d, *J*=15.1 Hz, Ar–CH_2–N), 3.13 (1H, m, H-1′′), 3.00 (1H, m, H-1′′), 2.30 (1H, m, *CH*(CH_3)$_2$), 1.14 (3H, d, *J*=6.9 Hz, CH_3), 0.87 (3H, d, *J*=6.9 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 165.8, 160.5, 150.6, 146.8, 135.6, 134.6, 131.1, 128.9, 128.4, 128.0, 126.9, 126.8, 120.2, 120.1, 60.1, 57.1, 45.7, 35.9, 33.4, 20.2, 17.7. Analysis calcd for $C_{24}H_{25}N_3O_2$: C, 74.39; H, 6.50; N, 10.84. Found: C, 74.21; H, 6.68; N, 10.51.

3.7. (1S,4S)-1-Allyl-2-benzyl-4-isopropyl-2,4-dihydro-1H-pyrazino[2,1-b]quinazoline-3,6-dione syn-**4**

Oil (petroleum ether:ethyl acetate 6:4). $[\alpha]_D$ +2.4 (0.25, chloroform). IR (NaCl) ν: 1681, 1603 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.27 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.72 (1H, ddd, *J*=8.3, 7.2, 1.5 Hz, H-9), 7.55 (1H, dd, *J*=8.3, 1.0 Hz, H-10), 7.46 (1H, ddd, *J*=8.0, 7.2, 1.0 Hz, H-8), 7.24 (5H, m, ArH), 5.96 (1H, ddt, *J*=17.0, 10.4, 7.0 Hz, H-2′′), 5.35 (1H, d, *J*=14.9 Hz, Ar–CH_2–N), 5.31 (1H, d, *J*=9.2 Hz, H-4), 5.17 (2H, m, H-3′′), 4.52 (1H, t, *J*=7.2 Hz, H-1), 4.20 (1H, d, *J*=14.9 Hz, Ar–CH_2–N), 2.77 (2H, m, H-1′′), 2.20 (1H, m, *CH*(CH_3)$_2$), 1.37 (3H, d, *J*=6.6 Hz, CH_3), 0.98 (3H, d, *J*=6.9 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 166.5, 161.2, 150.6, 146.8, 135.6, 134.6, 133.2, 128.9, 128.2, 128.0, 127.0, 126.9, 126.8, 120.0, 119.0, 60.2, 60.1, 48.5, 40.6, 34.2, 20.9, 19.1. Analysis calcd for $C_{24}H_{25}N_3O_2$: C, 74.39; H, 6.50; N, 10.84. Found: C, 74.36; H, 6.67; N, 10.26.

3.8. (4S)-2-Benzyl-1,1-diallyl-4-isopropyl-2,4-dihydro-1H-pyrazino[2,1-b]quinazoline-3,6-dione **10**

Oil (petroleum ether:ethyl acetate 6:4). Yield: 18%. $[\alpha]_D$ +17.3 (0.26, chloroform). IR (NaCl) ν: 1680, 1657, 1587 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.22 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.74 (1H, ddd, *J*=8.3, 7.0, 1.5 Hz, H-9), 7.64 (1H, dd, *J*=8.3, 1.3 Hz, H-10), 7.49 (2H, m, ArH), 7.46 (1H, ddd, *J*=8.0, 7.0, 1.3 Hz, H-8), 7.30 (3H, m, ArH), 5.48 (1H, m, H-2′′), 5.25 (1H, m, H-2′′′), 5.18 (1H, d, *J*=5.0 Hz, H-4), 5.16 (1H, d, *J*=15.1 Hz, Ar–CH_2–N), 4.88 (3H, m, 2H-3′′, H-3′′′), 4.70 (1H, dd, *J*=17.0, 1.6 Hz, H-3′′′), 4.50 (1H, d, *J*=15.1 Hz, Ar–CH_2–N), 3.24 (1H, dd, *J*=14.5, 8.0 Hz, H-1′′), 2.85 (3H, m, H-1′′, 2H-1′′′), 2.22 (1H, m, *CH*(CH_3)$_2$), 1.09 (3H, d, *J*=6.9 Hz, CH_3), 0.95 (3H, d, *J*=6.9 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 166.8,

160.9, 152.1, 146.8, 138.1, 134.5, 132.1, 130.0, 128.8, 128.5, 127.5, 127.0, 126.72, 126.70, 120.8, 120.1, 119.9, 70.0, 59.5, 46.2, 45.7, 42.8, 34.3, 20.1, 18.6. Analysis calcd for $C_{27}H_{29}N_3O_2$: C, 75.85; H, 6.84; N, 9.83. Found: C, 76.13; H, 7.22; N, 9.35.

3.9. *(1*R,*4*S*)-1,2-Dibenzyl-4-isopropyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione* anti-***5***

Mp: 135–137°C (CH_2Cl_2:ethyl acetate 9:1). $[\alpha]_D$ +79 (0.25, chloroform). IR (KBr) ν: 1688, 1651, 1597 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.17 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.75 (1H, ddd, *J*=8.3, 7.1, 1.5 Hz, H-9), 7.60 (1H, dd, *J*=8.3, 1.2 Hz, H-10), 7.45 (1H, ddd, *J*=8.0, 7.1, 1.2 Hz, H-8), 7.36 (5H, m, ArH), 7.12 (3H, m, ArH), 6.66 (2H, m, H-2′′,6′′), 5.75 (1H, d, *J*=14.7 Hz, Ar–CH_2–N), 4.86 (1H, dd, *J*=3.9, 3.5 Hz, H-1), 4.38 (1H, d, *J*=3.3 Hz, H-4), 4.13 (1H, d, *J*=14.7 Hz, Ar–CH_2–N), 3.52 (1H, dd, *J*=14.1, 3.9 Hz, C_1–CH_2–Ar), 3.28 (1H, dd, *J*=14.1, 3.5 Hz, C_1–CH_2–Ar), 2.13 (1H, m, *CH*(CH_3)$_2$), 1.12 (3H, d, *J*=7.0 Hz, CH_3), 0.67 (3H, d, *J*=7.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 165.0, 160.1, 150.5, 146.5, 135.1, 134.6, 133.7, 129.2, 129.0, 128.9, 128.6, 128.2, 127.7, 126.8, 126.7, 126.6, 120.3, 59.7, 58.5, 46.3, 39.0, 33.4, 20.3, 16.5. Analysis calcd for $C_{28}H_{27}N_3O_2$: C, 76.86; H, 6.22; N, 9.60. Found: C,77.05; H, 6.08; N, 9.53.

3.10. *(1*S,*4S)-1,2-Dibenzyl-4-isopropyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione* syn-***5***

Oil (CH_2Cl_2:ethyl acetate 9:1). $[\alpha]_D$ −3.2 (0.19, chloroform). IR (NaCl) ν: 1682, 1601 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.26 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.72 (1H, ddd, *J*=8.4, 7.1, 1.5 Hz, H-9), 7.52 (1H, dd, *J*=8.4, 1.1 Hz, H-10), 7.46 (1H, ddd, *J*=8.0, 7.1, 1.1 Hz, H-8), 7.35 (3H, m, ArH), 7.18 (2H, m, ArH), 7.35 (3H, m, ArH), 6.92 (2H, m, ArH), 6.66 (2H, m, H-2′′,6′′), 5.34 (1H, d, *J*=9.6 Hz, H-4), 5.26 (1H, d, *J*=14.9 Hz, Ar–CH_2–N), 4.69 (1H, dd, *J*=9.2, 5.0 Hz, H-1), 3.48 (1H, dd, *J*=13.7, 5.0 Hz, C_1–CH_2–Ar), 3.21 (1H, dd, *J*=13.7, 9.2 Hz, C_1–CH_2–Ar), 3.16 (1H, d, *J*=14.9 Hz, Ar–CH_2–N), 2.12 (1H, m, *CH*(CH_3)$_2$), 1.38 (3H, d, *J*=6.7 Hz, CH_3), 0.97 (3H, d, *J*=6.7 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 166.5, 161.1, 150.9, 146.7, 136.4, 135.3, 134.6, 129.4, 129.0, 128.7, 128.2, 127.8, 127.6, 127.1, 127.0, 126.7, 119.9, 61.8, 60.1, 48.1, 42.5, 34.3, 20.9, 19.4. Analysis calcd for $C_{28}H_{27}N_3O_2$: C, 76.86; H, 6.22; N, 9.60. Found: C, 76.82; H, 6.48; N, 9.71.

3.11. *(4*S*)-4-Isopropyl-1,1,2-tribenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione* ***11***

White solid (toluene:ethyl acetate 85:15). Mp: 144–145°C. $[\alpha]_D$ +10.6 (0.26, chloroform). IR (KBr) ν: 1687, 1656, 1588 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.18 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.85 (1H, ddd, *J*=8.4, 7.0, 1.5 Hz, H-9), 7.78 (1H, dd, *J*=8.2, 1.3 Hz, H-10), 7.50 (1H, ddd, *J*=8.0, 7.0, 1.3 Hz, H-8), 7.20 (5H, m, ArH), 7.00 (6H, m, ArH), 6.75 (2H, m, ArH), 6.55 (2H, m, ArH), 5.53 (1H, d, *J*=14.9 Hz, Ar–CH_2–N), 4.72 (1H, d, *J*=14.9 Hz, Ar–CH_2–N), 4.39 (1H, d, *J*=5.4 Hz, H-4), 4.18 (1H, d, *J*=14.3 Hz, C_1–CH_2–Ar), 3.67 (1H, d, *J*=13.9 Hz, C_1–CH_2–Ar), 3.56 (1H, d, *J*=13.9 Hz, C_1–CH_2–Ar), 3.50 (1H, d, *J*=14.3 Hz, C_1–CH_2–Ar), 1.44 (1H, m, *CH*(CH_3)$_2$), 0.72 (3H, d, *J*=6.9 Hz, CH_3), 0.39 (3H, d, *J*=6.9 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 167.0, 160.5, 151.9, 146.3, 138.2, 135.4, 134.6, 133.9, 131.2, 129.6, 129.0, 128.6, 128.2, 127.8, 127.7, 127.6, 126.9, 126.8, 126.7, 120.2, 72.7, 59.1, 48.7, 47.9, 43.8, 34.2, 20.1, 17.8. Analysis calcd for $C_{35}H_{33}N_3O_2$: C, 79.67; H, 6.30; N, 7.96. Found: C, 79.26; H, 6.16; N, 7.66.

*3.12. (1*R*,4*S*)-2-Benzyl-4-isopropyl-1-p-methylbenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione* anti-***6***

Mp: 147–149°C. $[\alpha]_D$ +68.8 (0.26, chloroform). IR (NaCl) ν: 1688, 1651, 1595 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.18 (1H, dd, *J*=8.1, 1.5 Hz, H-7), 7.75 (1H, ddd, *J*=8.4, 7.1, 1.5 Hz, H-9), 7.60 (1H, dd, *J*=8.4, 1.1 Hz, H-10), 7.46 (1H, ddd, *J*=8.1, 7.1, 1.1 Hz, H-8), 7.37 (5H, m, ArH), 6.90 (2H, d, *J*=7.9 Hz, H-3′,5′), 6.54 (2H, d, *J*=7.9 Hz, H-2′,6′), 5.75 (1H, d, *J*=14.7 Hz, Ar–CH_2–N), 4.83 (1H, dd, *J*=4.0, 3.3 Hz, H-1), 4.40 (1H, d, *J*=3.2 Hz, H-4), 4.12 (1H, d, *J*=14.7 Hz, Ar–CH_2–N), 3.49 (1H, dd, *J*=14.1, 4.0 Hz, C_1–CH_2–Ar), 3.24 (1H, dd, *J*=14.1, 3.3 Hz, C_1–CH_2–Ar), 2.22 (1H, s, CH_3Ar), 2.17 (1H, m, *CH*(CH_3)$_2$), 1.13 (3H, d, *J*=6.9 Hz, CH_3), 0.66 (3H, d, *J*=6.9 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 164.9, 160.1, 158.7, 146.6, 137.3, 135.1, 134.6, 130.4, 129.2, 129.0, 128.98, 128.93, 128.2, 126.8, 126.6, 120.3, 59.7, 58.6, 46.5, 38.3, 33.6, 21.2, 20.5, 16.7. Analysis calcd for $C_{29}H_{29}N_3O_2$: C, 77.14; H, 6.47; N, 9.31. Found: C, 77.12; H, 6.52; N, 9.27.

*3.13. (1*S*,4*S*)-2-Benzyl-4-isopropyl-1-p-methylbenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione* syn-***6***

$[\alpha]_D$ −5.8 (0.25, chloroform). IR (NaCl) ν: 1684, 1602 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.26 (1H, dd, *J*=8.1, 1.5 Hz, H-7), 7.72 (1H, ddd, *J*=8.4, 7.1, 1.5 Hz, H-9), 7.53 (1H, dd, *J*=8.4, 1.1 Hz, H-10), 7.45 (1H, ddd, *J*=8.1, 7.1, 1.1 Hz, H-8), 7.20 (5H, m, ArH), 7.15 (4H, t, *J*=8.0 Hz, ArH), 5.38 (1H, d, *J*=9.6 Hz, H-4), 5.25 (1H, d, *J*=14.9 Hz, Ar–CH_2–N), 4.66 (1H, dd, *J*=9.3, 4.9 Hz, H-1), 3.45 (1H, dd, *J*=13.8, 4.9 Hz, C_1–CH_2–Ar), 3.18 (1H, dd, *J*=13.8, 9.3 Hz, C_1–CH_2–Ar), 3.14 (1H, d, *J*=14.7 Hz, Ar–CH_2–N), 2.37 (1H, s, CH_3Ar), 2.11 (1H, m, *CH*(CH_3)$_2$), 1.38 (3H, d, *J*=6.8 Hz, CH_3), 0.96 (3H, d, *J*=6.8 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 166.5, 161.2, 151.1, 146.8, 137.3, 135.4, 134.6, 133.2, 129.7, 129.3, 128.7, 128.2, 127.8, 127.1, 126.9, 126.7, 120.0, 61.9, 60.1, 48.1, 42.0, 34.2, 21.1, 20.9, 19.3. Analysis calcd for $C_{29}H_{29}N_3O_2$: C, 77.14; H, 6.47; N, 9.31. Found: C, 77.39; H, 6.61; N, 9.28.

*3.14. (1*R*,4*S*)-2-Benzyl-4-isopropyl-1-p-nitrobenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione* anti-***7***

Mp: 114–116°C (yellow solid). $[\alpha]_D$ +67 (0.25, chloroform). IR (NaCl) ν: 1680, 1602 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.18 (1H, dd, *J*=8.0, 1.4 Hz, H-7), 7.95 (2H, d, *J*=8.7 Hz, H-3″,5″), 7.75 (1H, ddd, *J*=8.4, 7.1, 1.4 Hz, H-9), 7.57 (1H, dd, *J*=8.4, 1.2 Hz, H-10), 7.47 (1H, ddd, *J*=8.0, 7.1, 1.2 Hz, H-8), 7.35 (5H, m, ArH), 6.97 (2H, d, *J*=8.7 Hz, H-2″,6″), 5.72 (1H, d, *J*=15.1 Hz, Ar–CH_2–N), 4.95 (1H, dd, *J*=4.9, 3.6 Hz, H-1), 4.80 (1H, d, *J*=4.9 Hz, H-4), 4.16 (1H, d, *J*=15.1 Hz, Ar–CH_2–N), 3.66 (1H, dd, *J*=14.5, 4.9 Hz, C_1–CH_2–Ar), 3.56 (1H, dd, *J*=14.5, 3.6 Hz, C_1–CH_2–Ar), 2.19 (1H, m, *CH*(CH_3)$_2$), 1.09 (3H, d, *J*=6.7 Hz, CH_3),), 0.80 (3H, d, *J*=6.9 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 165.5, 160.1, 149.7, 146.9, 146.3, 142.8, 135.0, 134.9, 130.0, 129.1, 128.4, 128.3, 127.3, 126.9, 126.7, 59.9, 57.9, 46.4, 37.4, 33.0, 20.1, 17.2. Analysis calcd for $C_{28}H_{26}N_4O_4$: C, 69.70; H, 5.43; N, 11.61. Found: C, 69.66; H, 5.33; N, 11.43.

*3.15. (1*S*,4*S*)-2-Benzyl-4-isopropyl-1-p-nitrobenzyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione* syn-***7***

$[\alpha]_D$ +12.2 (0.25, chloroform). IR (NaCl) ν: 1679, 1602 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.26 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 8.18 (2H, d, *J*=8.7 Hz, H-3″,5″), 7.70 (1H, ddd, *J*=8.5, 7.2, 1.5 Hz, H-9), 7.47 (1H, ddd, *J*=8.0, 7.2, 1.2 Hz, H-8), 7.40 (1H, dd, *J*=8.5, 1.2 Hz, H-10), 7.35 (2H, d, *J*=8.7 Hz, H-2″,6″), 7.24

(3H, m, ArH), 7.07 (2H, m, ArH), 5.36 (1H, d, *J*=9.4 Hz, H-4), 5.16 (1H, d, *J*=14.9 Hz, Ar–CH_2–N), 4.70 (1H, dd, *J*=7.0, 6.7 Hz, H-1), 3.76 (1H, d, *J*=14.9 Hz, Ar–CH_2–N), 3.46 (1H, dd, *J*=13.8, 6.7 Hz, C_1–CH_2–Ar), 3.29 (1H, dd, *J*=13.8, 7.0 Hz, C_1–CH_2–Ar), 2.18 (1H, m, *CH*(CH_3)$_2$), 1.33 (3H, d, *J*=6.6 Hz, CH_3), 1.08 (3H, d, *J*=6.9 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 166.3, 161.0, 149.8, 147.2, 146.5, 144.1, 135.1, 134.8, 130.3, 129.0, 128.2, 128.1, 127.3, 127.1, 126.7, 123.9, 120.0, 61.7, 60.1, 48.6, 42.2, 34.4, 20.8, 19.3. Analysis calcd for $C_{28}H_{26}N_4O_4$: C, 69.70; H, 5.43; N, 11.61. Found: C, 69.99; H, 5.73; N, 11.30.

*3.16. (1*R*,4*S*)-2-Benzyl-1-m-chlorobenzyl-4-isopropyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione anti-**8***

[α]$_D$ +30.4 (0.25, chloroform). IR (NaCl) ν: 1679, 1599 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 8.20 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.75 (1H, ddd, *J*=8.4, 7.2, 1.5 Hz, H-9), 7.62 (1H, dd, *J*=8.4, 1.1 Hz, H-10), 7.47 (1H, ddd, *J*=8.1, 7.2, 1.1 Hz, H-8), 7.35 (2H, m, ArH), 7.20 (3H, m, ArH), 7.15 (1H, ddd, *J*=7.4, 2.0, 1.1 Hz, H-4′′), 7.06 (1H, t, *J*=7.4 Hz, H-5′′), 6.67 (1H, t, *J*=1.6 Hz, H-2′′), 6.66 (1H, dd, *J*=7.4, 1.6 Hz, H-5′′), 5.73 (1H, d, *J*=14.9 Hz, Ar–CH_2–N), 4.88 (1H, dd, *J*=4.2, 3.6 Hz, H-1), 4.64 (1H, d, *J*=4.0 Hz, H-4), 4.14 (1H, d, *J*=14.9 Hz, Ar–CH_2–N), 3.52 (1H, dd, *J*=14.2, 4.2 Hz, C_1–CH_2–Ar), 3.32 (1H, dd, *J*=14.2, 3.6 Hz, C_1–CH_2–Ar), 2.20 (1H, m, *CH*(CH_3)$_2$), 1.14 (3H, d, *J*=7.0 Hz, CH_3), 0.74 (3H, d, *J*=7.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 165.1, 160.1, 150.2, 146.4, 136.4, 135.1, 134.7, 134.3, 129.7, 129.4, 129.1, 128.7, 128.2, 128.1, 127.6, 127.0, 126.9, 126.7, 120.3, 59.7, 58.3, 46.4, 38.2, 33.3, 20.2, 16.8. Analysis calcd for $C_{28}H_{26}ClN_3O_2$: C, 71.25; H, 5.55; N, 8.90. Found: C, 71.18; H, 5.73; N, 8.65.

*3.17. (1*S*,4*S*)-2-Benzyl-1-m-chlorobenzyl-4-isopropyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione* syn-***8***

[α]$_D$ −0.4 (0.26, chloroform). IR (NaCl) ν: 1683, 1601 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 8.26 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.73 (1H, ddd, *J*=8.4, 7.2, 1.5 Hz, H-9), 7.52 (1H, dd, *J*=8.4, 1.1 Hz, H-10), 7.48 (1H, ddd, *J*=8.0, 7.2, 1.1 Hz, H-8), 7.22 (5H, m, ArH), 7.14 (2H,m, ArH), 6.98 (2H, m, ArH), 5.50 (1H, d, *J*=9.5 Hz, H-4), 5.35 (1H, d, *J*=14.9 Hz, Ar–CH_2–N), 4.68 (1H, dd, *J*=8.5, 5.3 Hz, H-1), 3.43 (1H, dd, *J*=13.8, 5.3 Hz, C_1–CH_2–Ar), 3.40 (1H, d, *J*=14.9 Hz, Ar–CH_2–N), 3.18 (1H, dd, *J*=13.9, 8.5 Hz, C_1–CH_2–Ar), 2.08 (1H, m, *CH*(CH_3)$_2$), 1.37 (3H, d, *J*=6.6 Hz, CH_3),), 0.97 (3H, d, *J*=6.8 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 166.4, 161.1, 150.5, 146.6, 138.5, 134.7, 134.6, 130.2, 129.5, 128.9, 128.2, 128.0, 127.7, 127.6, 127.1, 126.7, 120.2, 61.6, 60.1, 48.3, 42.1, 34.4, 20.8, 19.4. Analysis calcd for $C_{28}H_{26}ClN_3O_2$: C, 71.25; H, 5.55; N, 8.90. Found: C, 71.11; H, 5.73; N, 8.55.

*3.18. (1*R*,4*S*)-2-Benzyl-4-isopropyl-1-(2-naphthyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione* anti-***9***

[α]$_D$ +86 (0.26, chloroform). IR (NaCl) ν: 1680, 1599 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 8.17 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.79 (1H, ddd, *J*=8.1, 7.0, 1.5 Hz, H-9), 7.72 (1H, m, ArH), 7.65 (1H, dd, *J*=8.1, 1.1 Hz, H-10), 7.57 (3H, m, ArH), 7.48 (1H, ddd, *J*=8.0, 7.0, 1.1 Hz, H-8), 7.30 (7H, m, ArH), 7.19 (1H, s, H-1′′), 6.78 (1H, dd, *J*=8.3, 1.6 Hz, H-3′′), 5.77 (1H, d, *J*=14.8 Hz, Ar–CH_2–N), 4.98 (1H, dd, *J*=3.8, 3.5 Hz, H-1), 4.42 (1H, d, *J*=3.8 Hz, H-4), 4.25 (1H, d, *J*=14.9 Hz, Ar–CH_2–N), 3.71 (1H, dd, *J*=14.2, 3.8 Hz, C_1–CH_2–Ar), 3.51 (1H, dd, *J*=14.2, 3.5 Hz, C_1–CH_2–Ar), 2.15 (1H, m, *CH*(CH_3)$_2$), 1.08 (3H, d, *J*=6.9 Hz, CH_3),), 0.72 (3H, d, *J*=6.9 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 165.1, 160.0, 150.7, 146.6, 135.3, 134.7, 133.0, 132.3, 131.5, 129.0, 128.9, 128.8, 128.3, 128.2, 128.17, 128.1, 127.6, 127.3,

126.9, 126.8, 126.75, 126.7, 126.3, 126.0, 120.3, 59.7, 58.6, 46.4, 38.8, 33.2, 20.2, 16.7. Analysis calcd for $C_{32}H_{29}N_3O_2$: C, 78.83; H, 5.99; N, 8.62. Found: C, 78.43; H, 6.19, N, 8.34.

*3.19. (1*S*,4*S*)-2-Benzyl-4-isopropyl-1-(2-naphthyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione* syn-***9***

$[\alpha]_D$ +18.4 (0.25, chloroform). IR (NaCl) ν: 1684, 1600 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.27 (1H, dd, *J*=8.0, 1.5 Hz, H-7), 7.85 (2H, m, ArH), 7.73 (1H, ddd, *J*=8.4, 7.1, 1.5 Hz, H-9), 7.69 (1H, s, ArH), 7.54 (1H, dd, *J*=8.4, 1.3 Hz, H-10), 7.48 (4H, m, ArH), 7.44 (1H, ddd, *J*=8.0, 7.1, 1.3 Hz, H-8), 7.18 (3H, m, ArH), 6.88 (2H, m, ArH), 5.36 (1H, d, *J*=9.6 Hz, H-4), 5.21 (1H, d, *J*=14.9 Hz, Ar–CH_2–N), 4.83 (1H, dd, *J*=9.2, 4.8 Hz, H-1), 3.66 (1H, dd, *J*=13.8, 4.8 Hz, C_1–CH_2–Ar), 3.39 (1H, dd, *J*=13.8, 9.2 Hz, C_1–CH_2–Ar), 3.21 (1H, d, *J*=14.9 Hz, Ar–CH_2–N), 2.21 (1H, m, *CH*(CH_3)$_2$), 1.39 (3H, d, *J*=6.6 Hz, CH_3), 0.98 (3H, d, *J*=6.8 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 166.5, 161.2, 151.1, 146.7, 135.3, 134.7, 133.8, 133.4, 132.5, 128.8, 128.7, 128.2, 128.17, 127.8, 127.7, 127.6, 127.1, 127.08, 127.0, 126.7, 126.5, 126.1, 120.0, 61.8, 60.1, 48.3, 42.8, 34.3, 20.9, 19.3. Analysis calcd for $C_{32}H_{29}N_3O_2$: C, 78.83; H, 5.99; N, 8.62. Found: C, 78.50; H, 6.23; N, 8.31.

Acknowledgements

We thank CICYT for financial support (Project SAF97-0143).

References

1. Schöllkopf, U.; Groth, U.; Deng, C. *Angew. Chem., Int. Ed. Engl*. **1981**, *20*, 798–799.
2. For summaries of the alkylation of bis-lactim ethers, see: (a) Schöllkopf, U. *Tetrahedron* **1983**, *39*, 2085–2091. (b) Schöllkopf, U. *Pure & Appl. Chem*. **1983**, *55*, 1799–1806. (c) Schöllkopf, U. *Topics Curr. Chem*. **1983**, *109*, 65–84. (d) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1989; chapter 1.
3. See: (a) Williams, R. M.; Glinka, T.; Kwast, E. *J. Am. Chem. Soc.* **1988**, *110*, 5927–5929. (b) Williams, R. M.; Glinka, T.; Kwast, E.; Coffman, H.; Stille, J. K. *J. Am. Chem. Soc.* **1990**, *112*, 808–821. (c) Williams, R. M.; Kwast, E. *J. Org. Chem*. **1988**, *53*, 5785–5787. (d) Williams, R. M.; Durham, C. A. *Chem Rev.* **1988**, *88*, 511–540.
4. (a) Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1992**, *57*, 6532–6536. (b) Orena, M.; Porzi, G.; Sandri, S. *J. Chem. Research (S)* **1993**, 318–319. (c) Porzi, G.; Sandri, S. *Tetrahedron: Asymmetry* **1994**, *5*, 453–464. (d) D'Arrigo, M. C.; Porzi, G.; Rossetti, M.; Sandri, S. *J. Chem. Research (S)* **1995**, 162–163. (e) Porzi, G; Sandrini, S. *Tetrahedron: Asymmetry* **1996**, *7*, 189–196.
5. Bull, S. D.; Davies, S. G.; Epstein, S. W.; Ouzman, J. V. A. *Chem. Commun.* **1998**, 659–660.
6. Martín-Santamaría, S.; Buenadicha, F. L.; Espada, M.; Söllhuber, M.; Avendaño, C. *J. Org. Chem*. **1997**, *62*, 6424–6428.
7. Buenadicha, F. L.; Bartolomé, M. T.; Aguirre, M. J.; Avendaño, C.; Söllhuber, M. *Tetrahedron: Asymmetry* **1998**, *9*, 483–501.
8. (a) Biological activity: Karwowsky, J. P.; Jackson, M.; Rasmussen, R. R.; Humphrey, P. E.; Poddig, J. B.; Kohl, W. L.; Scherr, M. H.; Kadam, S.; McAlpine, J. B. *J. Antibiot*. **1993**, *46*, 374–379. (b) Isolation and structure: Hochlowki, J. E.; Mullally, M. M.; Spanton, S. G.; Whittern, D. N.; Hill, P.; McAlpine, J. B. *J. Antibiot*. **1993**, *46*, 380–386. (c) Total synthesis: Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc*. **1994**, *116*, 11143–11144.
9. Gottesman, M. M.; Pastan, I. *J. Biol. Chem*. **1988**, *263*, 12163–12166. (b) Endicott, J. A.; Ling, V. *Annu. Rev. Biochem*. **1989**, *58*, 137–171. (c) Gottesman, M. M.; Pastan, I. *Annu. Rev. Biochem*. **1993**, *62*, 385–427. (d) Patel, N. H.; Rothenberg, M. L. *Invest. New Drug* **1994**, *12*, 1–13.
10. Rodríguez de Quesada, A., personal communication.
11. Bartolomé, M. T.; Buenadicha, F. L.; Avendaño, C.; Söllhuber, M. *Tetrahedron: Asymmetry* **1998**, *9*, 249–258.