Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 411–418

TETRAHEDRON: *ASYMMETRY*

1-Bromo-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones as α-bromoglycine templates

María Luisa Heredia, María Fernández, Elena de la Cuesta and Carmen Avendaño*

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

Received 19 December 2000; accepted 8 February 2001

Abstract—The title compounds behaved as α-bromoglycine templates. Radical substitutions and S_N1-type nucleophilic additions proceeded with retention of stereochemistry, while S_N2-type displacements occurred with net inversion of configuration. A homocoupling product was obtained in attempting a Stille cross-coupling reaction. © 2001 Published by Elsevier Science Ltd.

1. Introduction

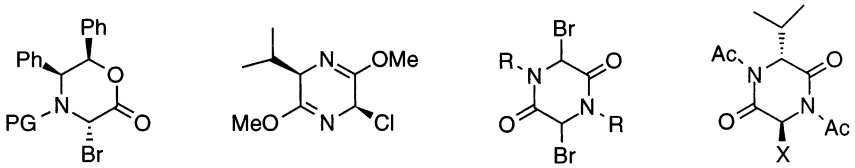
The use of α-haloglycine derivatives for the elaboration of glycine residues is extensively documented.[1] High diastereoselectivities, imposed by geometrical constraints, have been found for α-haloglycine templates such as those derived from *N*-protected (Cbz or BOC) *erythro*-5,6-diphenyl-3,4,5,6-tetrahydro-1,4-oxazin-2-ones **1**,[2,3] bislactim ethers **2**[4,5] and *N*,*N*′-dialkyl- **3**[6–12] or *N*,*N*′-diacylpiperazine-2,5-diones **4**[13,14] (Fig. 1).

Williams established that compounds **3** cannot directly be used as glycine templates due to extensive decomposition under a range of Lewis acid conditions, but found that they could be derived, for α-C-functionalisation, to their 3,6-bis(2′-thiopyridyl) analogues, which react with nucleophiles in the presence of thiophilic metal salts.[8,15] The intermediate iminium species thus formed were attacked in most cases from the same face of the piperazinedione nucleus as the departing thiopyridyl residue, giving *cis*-3,6-derivatives. However, α-haloglycine templates **4** gave *trans*-3,6-derivatives in reaction with the radical derived by bromine atom transfer.[14]

The use of 2,4-dialkyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones such as **5**, as nucleophilic[16–21] or electrophilic[22,23] glycine templates, is being developed in our group. This system contains rings D–F of the natural MDR (multi drug resistance) reversal agent *N*-acetylardeemin[24,25] and retains most of its biological activity.[26] Our interest in this chemotherapeutic property moved us to study new synthetic entries to derivatives of this system. Here, we study the α-bromoglycine templates **7** and **8**.

2. Results and discussion

Bromination of compounds **5**[16] and **6** under radical conditions afforded the bromides **7** and **8**, respectively, as single diastereoisomers (Scheme 1). All attempts to

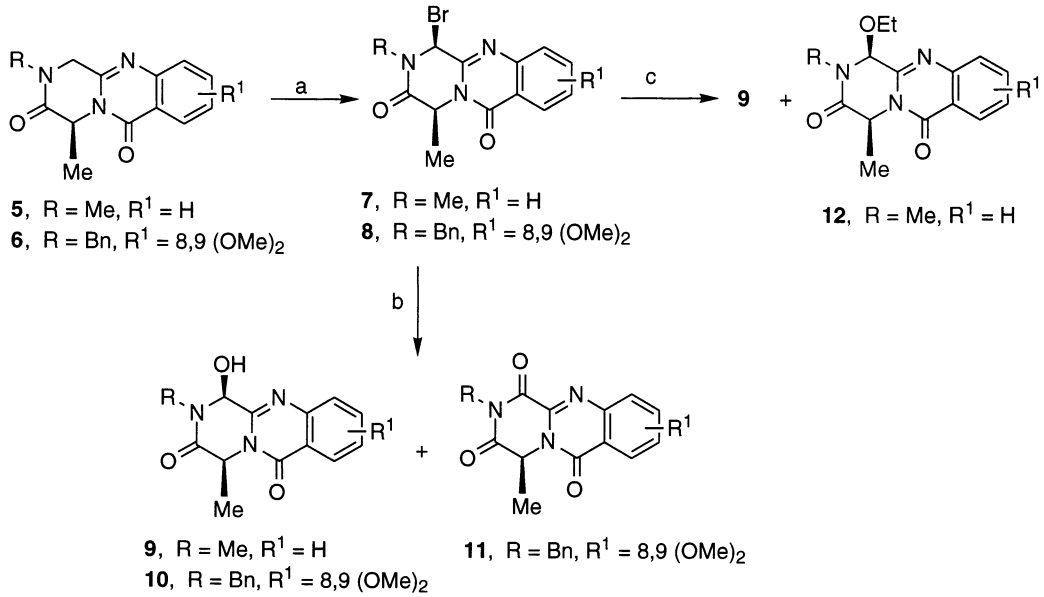


1, PG = Cbz, BOC **2** **3** **4**, X = Br, Cl

Figure 1. Some α-haloglycine templates.

* Corresponding author. Fax: 34 91 394 18 22; e-mail: avendano@eucmax.sim.ucm.es

0957-4166/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0957-4166(01)00067-2



Scheme 1. (a) NBS (1 equiv.), AIBN (1%) for **5** or $(PhCOO)_2$ (1%) for **6**, CCl_4, 2 h, reflux, rt. (b) Isolation of **7** and **8** and purification attempts by column chromatography. (c) Evaporation of a chloroform (stabilised with ethanol) solution of **7**.

study their stereochemistry were unsuccessful because of partial hydrolysis–oxidation to *cis*-1-hydroxy and 1-oxo derivatives (**9**–**11**). This decomposition occurred even on standing in carbon tetrachloride solution. Attempts to purify bromide **7** by evaporation of a chloroform solution followed by column chromatography gave **9** and the *cis*-1-ethoxy derivative **12** arising from a substitution reaction with ethanol present as a chloroform stabiliser. The *cis*-1,4-stereochemistry of compound **12** was established by NOE experiments (signal enhancements of $OC\underline{H}_2$ and $OCH_2\text{-}C\underline{H}_3$ protons after irradiation of the C-(4) methyl protons and vice versa). The stereochemistry of compounds **7** and **8** is discussed later.

The rapid decomposition of bromides **7** and **8** led to their use as crude products. The results obtained from some nucleophilic displacement reactions are summarised in Table 1.

Reactions with weak nucleophiles catalysed with strong Lewis acids (entries 1–4) gave compounds **13**–**16**, which showed a *cis* (**13**–**15**) or *trans* (**16**) 1,4-relationship (NOE experiments were conclusive in all compounds). These stereochemical results are in accordance with S_N1-type addition of the nucleophile to *N*-acyliminium intermediates **I** (Scheme 2). In our experience with experimental protocols starting with C-(1)-oxidation,[22] iminium species were diastereoselectively attacked by nucleophiles with retention of configuration. In this case, only the bulky trimethylsilylketene acetal of diethyl malonate (entry 4) gave the inverted product in order to minimise the 1,4-steric interactions. This also occurred in the iminium species derived from **4**.

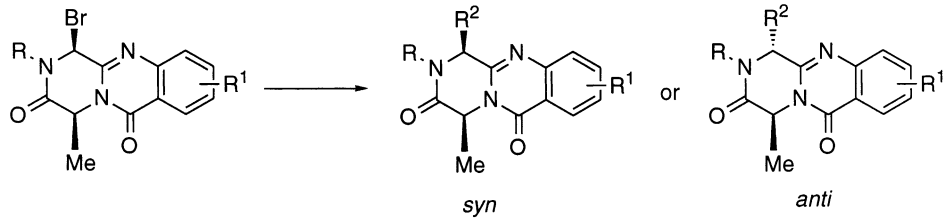
The reactions with good nucleophiles (entries 5–9) gave compounds **16**–**20** with a *trans*-1,4-stereochemistry (NOE experiments of compounds **17** and **18** showed an enhancement of the H-(1) signal after irradiation of the C-(4) methyl protons and vice versa), indicating net inversion of configuration and S_N2-type displacement of the bromine. Although this stereochemistry could be the result of thermodynamic control (excess nucleophile, room temperature and long reaction time), it has been clearly established in the more extensively studied enolate based chemistry of compounds **5** and **6**[16,18,19] that the 1,4-*trans*-disubstituted derivatives equilibrate to the more stable *cis*-isomers. Thus, the *trans*-isomers (compounds **16**–**20**, entries 5–9) obtained in these conditions are formed under kinetic control.

The enantiomeric purity of compound (+)-**17**, for which epimerisation of the C-(4)-stereocentre could be expected given the basicity of the nucleophile, was confirmed by chiral HPLC analysis, in comparison to a racemic sample obtained from (±)-**7**.

Entries 10 and 11 of Table 1 show the results obtained through radical mechanisms (intermediates **II**, Scheme 2), affording compounds **13** and **14**. The yields were better than those obtained in S_N1-type reactions (entries 1 and 2). When the benzene used as a solvent in these radical promoted substitutions was not properly deoxygenated, a substantial amount of the 1-phenoxy derivative **21** was isolated (entry 12). Its structure was confirmed by mass spectrometry and NMR experiments (long distance correlations between the H-(1) and C-(1′) phenyl resonances). This product must be formed in the reaction of a hydroperoxide intermediate with benzene.[27]

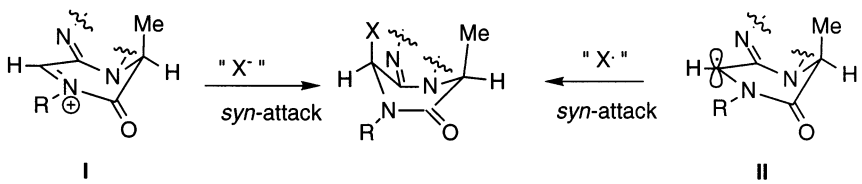
Since radical mechanisms imply kinetic control, bromides **7** and **8** (also obtained through intermediates **II**) must have the same *cis*-stereochemistry as compounds **13**, **14** and **21**. Furthermore, assuming that compounds **16**–**20** have been obtained by S_N2-type displacement,

Table 1. Substitution of a bromine atom in compounds **7** and **8**



Entry	Catalyst	Reagent	Diastereoselective attack (*d.e.* > 98%)	Comp. (% yield)	Starting bromide
1	$ZnCl_2$	Me_3Si	*syn*	**13** (41)	**7**
2	$ZnCl_2$	Me_3Si	*syn*	**14** (40)	**8**
3	$ZnCl_2$	O, CH_3	*syn*	**15** (68)	**7**
4	$ZnCl_2$	EtO_2CHC(=$OSiMe_3$)OEt	*anti*	**16** (85)	**7**
5	---	$PhS^- Na^+$	*anti*	**17** (60)	**7**
6	---	$PhS^- Na^+$	*anti*	**18** (80)	**8**
7		N, $S^- Na^+$	*anti*	**19** (95)	**7**
8	---	N, $S^- Na^+$	*anti*	**20** (65)	**8**
9	---	EtO_2CHC(=$O^- Na^+$)OEt	*anti*	**16** (72)	**7**
10	AIBN	Bu_3Sn	*syn*	**13** (85)	**7**
11	AIBN	Bu_3Sn	*syn*	**14** (60)	**8**
12	---	C_6H_6/O_2[a]	*syn*	**21** (68)	**7**

a) When reaction was performed without deoxygenation of the solvent.



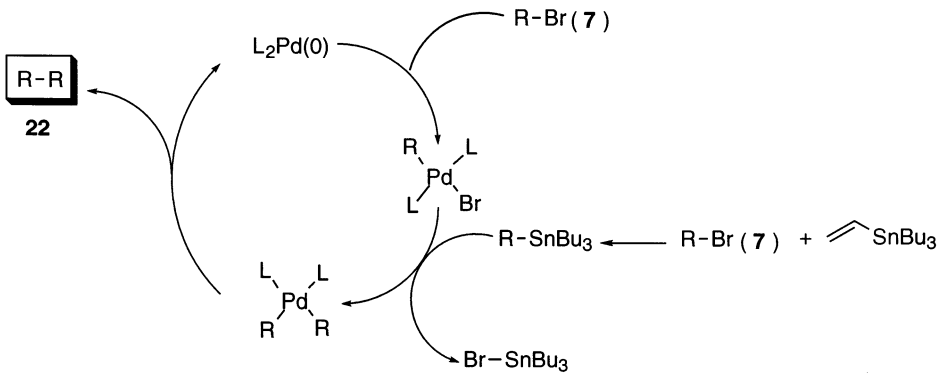
Scheme 2.

the single inversion of stereochemistry at C-(1) supports the *cis*-configuration for **7** and **8**.

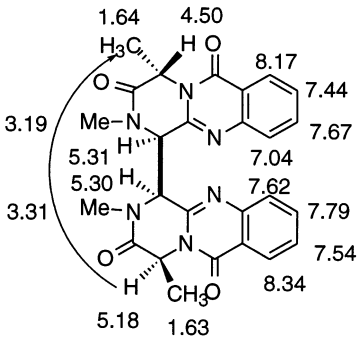
In a first attempt to achieve a cross-coupling reaction, we investigated the Stille-coupling between **7** and tributylvinyltin with Pd(0) as catalyst, but instead of the expected 1-vinyl derivative, the homocoupling product **22** (25%) was obtained. This compound must be formed through a previous transmetallation reaction (Scheme 3).

A $CDCl_3$ solution of compound **22** showed two sets of signals ascribed to non-equivalent moieties. Those corresponding to system **A** (Fig. 2) were similar to those of compounds so far described, while those of system **B**, and especially the H-(4′) proton, were more shielded. Furthermore, protons H-(1) and H-(1′) resonated as two nearly superimposed doublets with a coupling constant of 12.6 Hz, which is compatible with either a nearly eclipsed or staggered conformation around the C-(1)/C-(1′) bond.

The H-(4) and H-(4′) chemical shifts ($\delta = 5.18$ and 4.50 ppm, respectively) are indicative of a *cis*-1,4-relationship in system **A** and a *trans*-relationship in system **B**, since in other *cis*-2,4-dimethyl analogues substituted at



Scheme 3.



22

Figure 2.

C-(1), the H-(4) proton is deshielded because the C-(4) methyl group adopts a nearly axial disposition in the boat conformation of the pyrazine ring. Thus H-(4) is nearly coplanar to the carbonyl group at C-(6). This deshielding effect is not observed in the *trans*-1,4-isomers which are more planar.[16]

A conclusive NOE experiment showed, after irradiation of the H-(4) signal at 5.18 ppm (system **A**), enhancement of the 4′-methyl protons (system **B**), confirming the stereochemistry. The coupling of C-(1) and C-(1′) must be produced through a *syn*-attack in **A** and an *anti*-attack in **B** to give **22** in a folded conformation, with stereocentres (*S*)-C-(1) and (*R*)-C-(1′) nearly eclipsed. The *cis–trans*-stereochemistry in the pyrazine rings of system **A** and **B**, respectively, minimises the steric repulsion that would exist between methyl groups at C-(4) and C-(4′) in a *syn*-attack for both systems that would give a *cis*-relationship for 1,4- and 1′,4′-configurations (Fig. 2).

In conclusion, we have shown that the reactions of electrophilic glycine templates **7** and **8** are predictive in their scope and diastereoselectivity under different reaction mechanisms, and that this methodology provides a new approach to new derivatives of the pyrazinoquinazolinedione system.

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 disks. 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 microanalyser. Optical rotation measurements were obtained 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. Mass spectra were recorded on a Hewlett–Packard 5993C (EI, 70 eV) (Servicio de Espectroscopía U.C.M.). HPLC analysis was performed using a Constametric 4100 system equipped with a chiral column (Chiralcel OD) and UV–vis detector. Mobile phase: hexane/2-propanol (90:10).

3.1. (+)-(4*S*)-2-Benzyl-8,9-dimethoxy-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 6

A mixture of 1-benzyl-3-methylpiperazine-2,5-dione[16] (0.45 g, 2 mmol), triethyloxonium tetrafluoroborate (1.14 g, 6 mmol) and anhydrous Na_2CO_3 (1.06 g, 10 mmol) in dry CH_2Cl_2 (20 mL) was stirred overnight at room temperature, poured on ice-water, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4 and evaporated. 4,5-Dimethoxyanthranilic acid (0.4 g, 2 mmol) was added to the syrupy residue and the mixture was stirred vigorously at 110°C for 4 h under argon. The mixture was dissolved in EtOAc, extracted with diluted ammo-

nium hydroxide, dried (Na_2SO_4) and concentrated. Column chromatography of the evaporation residue (EtOAc, silica gel) afforded **6** as a white solid; yield 95%; mp 175–176°C; $[\alpha]_D^{25}=+52$ (c 0.15, $CHCl_3$); ν_{max} (KBr): 1671, 1607 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 7.53 (s, 1H), 7.36–7.24 (m, 5H), 6.91 (s, 1H), 5.51 (q, 1H, $J=7.1$ Hz), 4.83 (d, 1H, $J=14.5$ Hz), 4.51 (m, 2H), 4.24 (d, 1H, $J=14.5$ Hz), 3.94 (s, 3H), 3.92 (s, 3H), 1.58 (d, 3H, $J=7.1$ Hz); δ_C (63 MHz, $CDCl_3$) 167.7, 159.3, 155.3, 149.4, 146.6, 143.5, 135.2, 129.2, 128.4, 128.3, 113.9, 107.3, 105.7, 56.5, 56.4, 52.1, 49.7, 49.1, 17.3; $C_{21}H_{21}N_3O_4$ requires: C, 66.47; H, 5.57; N, 11.07. Found: C, 66.36; H, 5.89; N, 10.95%.

3.2. General procedure for the preparation of bromides 7 and 8

To a stirred solution of **5**[16] or **6** (1.0 equiv.) in CCl_4 (0.1 M) under nitrogen was added *N*-bromosuccinimide (1.1 equiv.) and a catalytic amount (1 mol%) of azobisisobutylnitrile for **5** or benzoyl peroxide for **6**. The mixture was refluxed for 2 h, cooled to room temperature, filtered and concentrated. The crude product was used without purification; otherwise, oxidation products **9**–**11** formed and were isolated by column chromatography.

Compound **12** was obtained with **9** from evaporation of a chloroform solution of **7** followed by column chromatography.

3.2.1. (+)-(1*S*,4*S*)-2,4-Dimethyl-1-hydroxy-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 9. **9** was obtained (EtOAc, silica gel) as a white solid; yield: 20%; mp 200–202°C; $[\alpha]_D^{25}=+55$ (c 0.35, $CHCl_3$); ν_{max} (KBr): 3520, 1685, 1660 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.32 (d, 1H, $J=7.8$ Hz), 7.81 (t, 1H, $J=8.3$ Hz), 7.67 (d, 1H, $J=7.4$ Hz), 7.53 (t, 1H, $J=8.2$ Hz), 5.80 (s, 1H), 5.37 (q, 1H, $J=7.0$ Hz), 4.97 (s, 1H), 3.22 (s, 3H), 1.80 (d, 3H, $J=7.0$ Hz); δ_C (63 MHz, $CDCl_3$) 169.5, 159.9, 149.3, 146.8, 135.0, 128.0, 127.1, 127.0, 121.0, 114.2, 82.8, 52.7, 32.9, 19.5; $C_{13}H_{13}N_3O_3$ requires: C, 60.22; H, 5.05; N, 16.20. Found: C, 60.38; H, 5.28; N, 16.42%.

3.2.2. (+)-(1*S*,4*S*)-2-Benzyl-1-hydroxy-8,9-dimethoxy-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 10. **10** was obtained (EtOAc/hexane 2:1, silica gel) as a white solid; yield: 15%; mp 119–120°C; $[\alpha]_D^{25}=+56$ (c 0.17, $CHCl_3$); ν_{max} (KBr): 3274, 1675, 1610 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 7.54 (s, 1H), 7.34–7.23 (m, 5H), 6.98 (s, 1H), 5.64 (d, 1H, $J=3.3$ Hz), 5.44 (q, 1H, $J=7.0$ Hz), 5.15 (d, 1H, $J=14.8$ Hz), 5.04 (d, 1H, $J=3.3$ Hz), 4.45 (d, 1H, $J=14.8$ Hz), 3.95 (s, 3H), 3.91 (s, 3H), 1.81 (d, 3H, $J=7.0$ Hz); δ_C (63 MHz, $CDCl_3$) 169.5, 159.2, 155.4, 149.8, 148.1, 142.9, 135.7, 129.2, 128.6, 128.4, 114.2, 107.2, 105.7, 79.8, 56.5, 52.7, 47.9, 19.6; $C_{21}H_{21}N_3O_5$ requires: C, 63.78; H, 5.35; N, 10.66. Found: C, 63.45; H, 5.28; N, 10.36%.

3.2.3. (−)-(4*S*)-2-Benzyl-8,9-dimethoxy-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-1,3,6-trione 11. **11** was obtained (EtOAc/hexane 2:1, silica gel) as a white solid; yield: 20%; mp 210–211°C; $[\alpha]_D^{25}=-24$ (c 0.05, $CHCl_3$); ν_{max} (KBr): 1736, 1679, 1609 cm^{-1}; δ_H (DMSO-d_6, 250 MHz) 7.51 (s, 1H), 7.39–7.25 (m, 5H), 7.34 (s, 1H), 5.27 (q, 1H, $J=7.0$ Hz), 5.03 (s, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 1.65 (d, 3H, $J=7.0$ Hz); δ_C (63 MHz, DMSO-d_6) 169.3, 158.3, 157.1, 155.3, 150.7, 142.6, 138.4, 136.2, 128.5, 127.6, 127.5, 115.2, 109.3, 105.2, 79.4, 56.5, 56.2, 19.6; $C_{21}H_{19}N_3O_5$ requires: C, 64.11; H, 4.87; N, 10.68. Found: C, 63.95; H, 4.63; N, 10.28%.

3.2.4. (+)-(1*S*,4*S*)-1-Ethoxy-2,4-dimethyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 12. **12** was obtained (EtOAc/hexane 2:3, aluminium oxide) as a white solid; yield: 20%; mp 115–117°C; $[\alpha]_D^{25}=+120$ (c 0.26, $CHCl_3$); ν_{max} (KBr): 1684, 1609 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.28 (dd, 1H, $J=7.9$ and 1.4 Hz), 7.77 (ddd, 1H, $J=8.1$, 7.4 and 1.4 Hz), 7.68 (dd, 1H, $J=8.1$ and 1.4 Hz), 7.51 (ddd, 1H, $J=7.9$, 7.4 and 1.4 Hz), 5.28 (q, 1H, $J=7.0$ Hz), 5.27 (s, 1H), 3.78 (q, 2H, $J=7.0$ Hz), 3.16 (s, 3H), 1.74 (d, 3H, $J=7.0$ Hz), 1.19 (t, 3H, $J=7.0$ Hz); δ_C (63 MHz, $CDCl_3$) 169.9, 160.2, 147.3, 147.0, 134.8, 127.8, 127.6, 126.9, 121.0, 88.9, 65.3, 52.9, 33.6, 19.2, 15.1; $C_{15}H_{17}N_3O_3$ requires: C, 62.71; H, 5.96; N, 14.62. Found: C, 62.73; H, 6.12; N, 14.93%.

3.3. General procedure for S_N1-type nucleophilic addition to bromides 7 and 8

To a stirred solution of unpurified **7** or **8** (1 equiv., 0.82 mmol) in dry THF (10 mL) at room temperature under argon was added the corresponding nucleophile (allyltrimethyl silane, 2-methylfuran or the trimethylsilylketene acetal of diethyl malonate[2]) (4 equiv.), followed by addition of a solution of $ZnCl_2$ in THF (0.5 M, 2 equiv., 1.64 mmol). After 12 h the mixture was poured into saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The combined organic extract was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography to afford compounds **13**–**16**.

3.3.1. (+)-(1*S*,4*S*)-1-Allyl-2,4-dimethyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 13. **13** was obtained (EtOAc/hexane 2:1, aluminium oxide) as a white solid; yield: 41%; mp 193–194°C; $[\alpha]_D^{25}=+49$ (c 0.12, $CHCl_3$); ν_{max} (KBr): 1671, 1598 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.25 (dd, 1H, $J=7.9$ and 1.5 Hz), 7.75 (ddd, 1H, $J=8.2$, 7.5 and 1.5 Hz), 7.61 (dd, 1H, $J=8.2$ and 1.2 Hz), 7.47 (ddd, 1H, $J=7.9$, 7.5 and 1.2 Hz), 5.87 (m, 1H), 5.28 (q, 1H, $J=7.2$ Hz), 5.2 (m, 2H), 4.56 (t, 1H, $J=6.8$ Hz), 3.11 (s, 3H), 2.82 (t, 2H, $J=6.8$ Hz), 1.73 (d, 3H, $J=7.2$ Hz); δ_C (63 MHz, $CDCl_3$) 167.1, 160.3, 150.1, 146.9, 134.9, 132.2, 127.2, 127.1, 126.8, 120.1, 119.9, 63.4, 52.4, 40.6, 34.3, 19.3; $C_{16}H_{17}N_3O_2$ requires: C, 67.83; H, 6.05; N, 14.83. Found: C, 67.78; H, 6.01; N, 14.9%.

3.3.2. (+)-(1*S*,4*S*)-1-Allyl-2-benzyl-8,9-dimethoxy-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 14. **14** was obtained (EtOAc/hexane 1:2, aluminium oxide) as a white solid; yield: 40%; mp 150–151°C; $[\alpha]_D^{25}=+16$ (c 0.15, $CHCl_3$); ν_{max} (KBr): 3274, 1675,

1610 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 7.55 (s, 1H), 7.30–7.23 (m, 5H), 6.97 (s, 1H), 5.44 (d, 1H, $J=14.9$ Hz), 5.40 (q, 1H, $J=7.1$ Hz), 5.14 (m, 2H), 4.54 (t, 1H, $J=6.6$ Hz), 4.13 (d, 1H, $J=14.9$ Hz), 3.99 (s, 3H), 3.96 (s, 3H), 2.97 (t, 1H, $J=6.9$ Hz), 1.79 (d, 3H, $J=7.1$ Hz); δ_C (63 MHz, $CDCl_3$) 167.6, 159.8, 155.4, 149.4, 148.9, 143.5, 135.4, 132.6, 129.1, 128.5, 128.3, 119.9, 113.8, 107.3, 105.5, 59.8, 56.5, 56.4, 52.4, 48.2, 40.7, 19.7; $C_{24}H_{25}N_3O_4$ requires: C, 68.72; H, 6.01; N, 10.02. Found: C, 68.69; H, 6.07; N, 9.98%.

3.3.3. (+)-(1*R*,4*S*)-2,4-Dimethyl-1(5-methyl-2-furyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 15. **15** was obtained (EtOAc/hexane 2:1, aluminium oxide) as a white solid; yield: 68%; mp 180–181°C; $[\alpha]_D^{25}=+31$ (*c* 0.17, $CHCl_3$); ν_{max} (KBr): 1690, 1589 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.27 (dd, 1H, $J=8.0$ and 1.5 Hz), 7.75 (ddd, 1H, $J=8.2$, 7.0 and 1.5 Hz), 7.66 (dd, 1H, $J=8.2$ and 1.3 Hz), 7.48 (ddd, 1H, $J=8.0$, 7.0 and 1.3 Hz), 6.27 (d, 1H, $J=3.1$ Hz), 5.94 (d, 1H, $J=3.1$ Hz), 5.57 (s, 1H), 5.36 (q, 1H, $J=7.1$ Hz), 3.14 (s, 3H), 2.2 (s, 3H), 1.69 (d, 3H, $J=7.1$ Hz); δ_C (63 MHz, $CDCl_3$) 167.8, 160.4, 153.8, 147.7, 147.3, 146.4, 134.8, 127.4, 127.2, 126.9, 120.5, 110.8, 106.9, 61.1, 52.7, 33.4, 18.2, 13.7; $C_{18}H_{17}N_3O_3$ requires: C, 66.86; H, 5.29; N, 12.99. Found: C, 66.80; H, 5.32; N, 13.02%.

3.3.4. (+)-(1*R*,4*S*)-1-Bis(ethoxycarbonyl)methyl-2,4-dimethyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 16. **16** was obtained (EtOAc/hexane 2:1, silica gel) as a white solid; yield: 85%; mp 46–48°C; $[\alpha]_D^{25}=+49$ (*c* 0.21, $CHCl_3$); ν_{max} (KBr): 1734, 1676 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.24 (dd, 1H, $J=8.2$ and 1.5 Hz), 7.70 (dt, 1H, $J=7.7$ and 1.3 Hz), 7.45 (m, 2H), 5.36 (d, 1H, $J=3.8$ Hz), 5.27 (q, 1H, $J=6.9$ Hz), 4.36 (d, 1H, $J=3.8$ Hz), 4.3 (m, 2H), 4.15 (m, 2H), 3.0 (s, 3H), 1.63 (d, 3H, $J=6.9$ Hz), 1.23 (t, 3H, $J=7.1$ Hz), 1.14 (t, 3H, $J=7.1$ Hz); δ_C (63 MHz, $CDCl_3$) 167.8, 166.1, 166.0, 160.1, 147.6, 146.2, 134.5, 127.0, 126.7, 126.6, 120.5, 62.0, 59.9, 53.9, 51.9, 31.9, 19.6, 13.9, 13.8; $C_{20}H_{23}N_3O_6$ requires: C, 59.84; H, 5.77; N, 10.47. Found: C, 60.16; H, 5.52; N, 10.71%.

3.4. General procedure for direct S_N2-type displacement of bromides 7 and 8

To a stirred suspension of NaH (1.2 equiv., 0.98 mmol) in dry THF (5 mL) at 0°C under argon, the nucleophile (1.2 equiv., 0.98 mmol) dissolved in dry THF was added. To the resultant mixture was added after 10 min a solution of compounds **7** or **8** (1 equiv., 0.82 mmol) in dry THF (10 mL). This solution was allowed to stir for 2 h at 0°C and at room temperature overnight. The mixture was quenched with a saturated ammonium chloride solution, and extracted with ethyl acetate, the combined organic layers were washed with sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate, filtered and concentrated. Chromatography of the residue on silica gel or aluminium oxide provided compounds **16** (72% yield) and **17**–**20**.

3.4.1. (+)-(1*R*,4*S*)-2,4-Dimethyl-1-phenylthio-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 17. **17** was obtained (EtOAc/hexane 2:3, aluminium oxide) as a yellow solid; yield: 60%; mp 159–161°C; $[\alpha]_D^{25}=+227$ (*c* 0.22, $CHCl_3$); ν_{max} (KBr): 1677, 1601 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.25 (dd, 1H, $J=7.8$ and 1.5 Hz), 7.71 (ddd, 1H, $J=8.4$, 7.6 and 1.5 Hz), 7.59 (m, 2H), 7.49–7.43 (m, 2H), 7.38–7.30 (m, 3H), 5.58 (s, 1H), 5.33 (q, 1H, $J=7.2$ Hz), 3.10 (s, 3H), 1.84 (d, 3H, $J=7.2$ Hz); δ_C (63 MHz, $CDCl_3$) 168.0, 160.3, 148.5, 147.2, 135.0, 134.8, 132.2, 129.6, 129.5, 127.5, 127.4, 126.9, 120.5, 71.5, 52.7, 33.2, 19.1; $C_{19}H_{17}N_3O_2S$ requires: C, 64.94; H, 4.88; N, 11.96. Found: C, 64.92; H, 5.22; N, 11.62%.

3.4.2. (+)-(1*R*,4*S*)-2-Benzyl-8,9-dimethoxy-4-methyl-1-phenylthio-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 18. **18** was obtained (EtOAc/CH_2Cl_2 4:3, silica gel) as a white solid; yield: 80%; mp 92–93°C; $[\alpha]_D^{25}=+179$ (*c* 0.23, $CHCl_3$); ν_{max} (KBr): 1674, 1610, 1594 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 7.47 (s, 1H), 7.44–7.07 (m, 5H), 7.26–7.20 (m, 3H), 7.06 (d, 2H, $J=8.0$ Hz), 7.04 (s, 1H), 5.74 (d, 1H, $J=14.4$ Hz), 5.54 (s, 1H), 4.41 (d, 1H, $J=14.4$ Hz), 3.97 (s, 3H), 3.96 (s, 3H), 3.83 (q, 1H, $J=6.6$ Hz), 1.49 (d, 3H, $J=6.6$ Hz); δ_C (63 MHz, $CDCl_3$) 167.5, 159.0, 155.4, 149.4, 146.7, 143.0, 137.4, 134.6, 131.1, 129.3, 129.2, 128.9, 128.6, 126.8, 113.6, 107.1, 105.4, 66.6, 56.3, 56.2, 52.1, 46.3, 21.2; $C_{27}H_{25}N_3O_4S$ requires: C, 66.51; H, 5.17; N, 8.62. Found: C, 66.69; H, 5.20; N, 8.31%.

3.4.3. (+)-(1*R*,4*S*)-2,4-Dimethyl-1(2′-pyridylthio)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 19. **19** was obtained (EtOAc/hexane 1:1, aluminium oxide) as a yellow solid; yield: 95%; mp 62–64°C; $[\alpha]_D^{25}=+405$ (*c* 0.27, $CHCl_3$); ν_{max} (KBr): 1680, 1602 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.55 (ddd, 1H, $J=4.5$, 1.6 and 0.8 Hz), 8.20 (dd, 1H, $J=8.0$ and 1.5 Hz), 7.65 (ddd, 1H, $J=8.1$, 7.5 and 1.5 Hz), 7.54–7.51 (m, 2H), 7.41 (ddd, 1H, $J=8.0$, 7.5 and 1.2 Hz), 7.29 (s, 1H), 7.14 (m, 2H), 5.39 (q, 1H, $J=7.2$ Hz), 3.09 (s, 3H), 1.76 (d, 3H, $J=7.2$ Hz); δ_C (63 MHz, $CDCl_3$) 168.4, 159.9, 154.4, 149.5, 148.9, 147.3, 137.0, 134.5, 127.4, 127.2, 126.6, 122.8, 121.3, 120.2, 64.1, 52.2, 31.8, 19.0. $C_{18}H_{16}N_4O_2S$ requires: C, 61.35; H, 4.58; N, 15.89. Found: C, 61.47; H, 4.46; N, 15.89%.

3.4.4. (+)-(1*R*,4*S*)-2-Benzyl-8,9-dimethoxy-4-methyl-1-(2′-pyridylthio)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 20. It was obtained (EtOAc/CH_2Cl_2 4:3, silica gel) as a white solid; yield: 65%; mp 170–171°C; $[\alpha]_D^{25}=+520$ (*c* 0.06, $CHCl_3$); ν_{max} (KBr): 1670, 1610 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.57 (dd, 1H, $J=4.0$ and 0.9 Hz), 7.60 (dt, 1H, $J=7.9$ and 1.8 Hz), 7.58 (s, 1H), 7.33–7.15 (m, 7H), 7.26 (s, 1H), 6.94 (s, 1H), 5.55 (q, 1H, $J=7.2$ Hz), 5.37 (d, 1H, $J=14.7$ Hz), 4.18 (d, 1H, $J=14.7$ Hz), 3.99 (s, 3H), 3.89 (s, 3H), 1.86 (d, 3H, $J=7.2$ Hz); δ_C (63 MHz, $CDCl_3$) 168.3, 159.3, 154.9, 154.7, 149.5, 149.4, 147.8, 143.7, 137.0, 135.7, 128.6, 127.8, 122.7, 121.2, 119.9, 113.7, 107.8, 105.3, 62.3, 56.3, 56.2, 52.2, 46.7, 19.3. $C_{26}H_{24}N_4O_4S$ requires: C, 63.92; H, 4.95; N, 11.47. Found: C, 63.96; H, 4.92; N, 11.30%.

3.5. General procedure for radical substitution of bromides 7 and 8

A solution of bromide **7** or **8** (0.82 mmol) in dry deoxygenated benzene (5 mL) under argon was treated with allyltributyltin (1.1 equiv., 0.9 mmol) at reflux for 1.5 h, with azobisisobutylnitrile to initiate the reaction. After removal of the solvent, the residue was dissolved in CH_2Cl_2, washed with brine and the organic solution was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography giving compounds **13** (85% yield) or **14** (60% yield).

The first experiments with compound **7** using dry benzene as solvent gave compound **21**.

3.5.1. (+)-(1*S*,4*S*)-2,4-Dimethyl-1-phenoxy-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione 21. It was obtained (EtOAc/hexane 1:1, aluminium oxide) as a white solid; yield: 68%; mp 98–100°C; $[\alpha]_D^{25}=+164$ (*c* 0.29, $CHCl_3$); ν_{max} (KBr): 1732, 1690 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.26 (dd, 1H, $J=8.0$ and 1.4 Hz), 7.95 (dd, 2H, $J=7.9$ and 1.3 Hz), 7.74 (ddd, 1H, $J=8.2$, 7.4 and 1.4 Hz), 7.66 (dd, 1H, $J=8.2$ and 1.4 Hz), 7.55 (dd, 1H, $J=7.0$ and 1.3 Hz), 7.47 (ddd, 1H, $J=8.0$, 7.4 and 1.4 Hz), 7.40 (dd, 2H, $J=7.9$ and 7.0 Hz), 7.19 (s, 1H), 5.44 (q, 1H, $J=7.1$ Hz), 3.23 (s, 3H), 1.88 (d, 3H, $J=7.1$ Hz); δ_C (63 MHz, $CDCl_3$) 169.8, 165.2, 159.9, 147.1, 145.6, 134.9, 134.2, 130.0, 128.8, 128.2, 127.9, 126.9, 121.0, 82.0, 52.7, 33.8, 19.6. $C_{19}H_{17}N_3O_3$ requires: C, 68.05; H, 5.11; N, 12.53. Found: C, 68.41; H, 4.75; N, 12.70%.

3.5.2. (+)-1,1′-Bi[(4*S*)-2,4-dimethyl-3,6-dioxo-2,3,4,6-tetrahydro-1*H*-pyrazino[2,1-*b*]quinazolinyl] 22. $Pd_2(dba)_3\cdot CHCl_3$ (0.04 equiv., 0.025 mmol, 26 mg) and $AsPh_3$ (0.3 equiv., 0.19 mmol, 61 mg) were stirred in dry THF at room temperature for 10 min. The crude bromo derivative **7** (1 equiv., 0.62 mmol) and the tributylvinyltin (1.1 equiv., 0.22 mmol, 0.19 mL) were dissolved in THF and added to the solution of the catalyst. The reaction mixture was stirred under reflux for 5 h, cooled to room temperature, washed with brine and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated. Silica gel chromatography of the residue with EtOAc gave a white solid (25% yield); mp 96–98°C; $[\alpha]_D^{25}=+41$ (*c* 0.19, $CHCl_3$); ν_{max} (KBr): 1669, 1597, 1567 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.34 (dd, 1H, $J=8.0$ and 1.2 Hz), 8.17 (dd, 1H, $J=7.9$ and 1.3 Hz), 7.79 (ddd, 1H, $J=8.2$, 7.5 and 1.5 Hz), 7.67 (ddd, 1H, $J=7.9$, 7.8 and 1.5 Hz), 7.62 (d, 1H, $J=8.2$ Hz), 7.54 (ddd, 1H, $J=8.0$, 7.5 and 1.1 Hz), 7.44 (ddd, 1H, $J=7.9$, 7.7 and 1.0 Hz), 7.04 (d, 1H, $J=7.9$ Hz), 5.31 (d, 1H, $J=12.6$ Hz), 5.30 (d, 1H, $J=12.6$ Hz), 5.18 (q, 1H, $J=7.1$ Hz), 4.50 (q, 1H, $J=6.6$ Hz), 3.31 (s, 3H), 3.19 (s, 3H), 1.64 (d, 3H, $J=6.6$ Hz), 1.63 (d, 3H, $J=7.1$ Hz); δ_C (63 MHz, $CDCl_3$) 167.8, 166.9, 161.2, 160.0, 147.5, 146.8, 145.8, 145.2, 135.3, 134.9, 128.0, 127.5, 127.1, 127.0, 126.9, 126.8, 124.3, 121.2, 70.0, 64.1, 52.7, 51.9, 36.1, 33.5, 20.4, 18.6. $C_{26}H_{24}N_6O_4$ requires: C, 64.45; H, 4.99; N, 17.35. Found: C, 64.19; H, 5.16; N, 17.41%.

Acknowledgements

Financial support from CICYT (SAF-97-0143 and SAF-94-0517) and an MEC fellowship (M.L.H.) are gratefully acknowledged.

References

1. For a review, see: Williams, R. M. In *Synthesis of Optically Active α-Amino Acids*, *Organic Chemistry Series*; Baldwin, J. E.; Magnus, P. D., Eds.; Pergamon Press, 1989; Vol. 7.
2. Williams, R. M.; Sinclair, P. J.; Zhai, W. *J. Am. Chem. Soc.* **1988**, *110*, 482–483.
3. Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547–1557.
4. Shöllkopf, U.; Neubauer, H. J.; Hauptreif, M. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1066–1067.
5. Shöllkopf, U.; Grüttner, S.; Anderskewitz, R.; Egert, E.; Dyrbusch, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 683–684.
6. Yoshimura, J.; Nakamura, H.; Matsunari, K. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 605–609.
7. Yoshimura, J.; Sugiyama, Y.; Nakamura, H. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2850–2853.
8. Williams, R. M.; Armstrong, R. W.; Maruyama, L. K.; Dung, J.-S.; Anderson, O. P. *J. Am. Chem. Soc.* **1985**, *107*, 3246–3253.
9. Williams, R. M.; Kwast, A. *J. Org. Chem.* **1988**, *53*, 5785–5789.
10. Badran, T. W.; Easton, Ch. J. *Aust. J. Chem.* **1990**, *43*, 1455–1459.
11. Badran, T. W.; Chai, C. L. L.; Easton, Ch. J.; Harper, J. B.; Page, D. M. *Aust. J. Chem.* **1995**, *48*, 1379–1384.
12. Whitlock, C. R.; Cava, M. P. *Tetrahedron Lett.* **1994**, *35*, 371–374.
13. Chai, C. L. L.; Page, D. M. *Tetrahedron Lett.* **1993**, *34*, 4373–4376.
14. Badran, T. W.; Easton, Ch. J.; Horn, E.; Kociuba, K.; May, B. L.; Schliebs, D. M.; Tiekink, E. R. T. *Tetrahedron: Asymmetry* **1993**, *4*, 197–200.
15. Williams, R. M.; Armstrong, R. W.; Dung, J.-S. *J. Am. Chem. Soc.* **1984**, *106*, 5748–5750.
16. Martin-Santamaría, S.; Buenadicha, F.; Espada, M.; Söllhuber, M.; Avendaño, C. *J. Org. Chem.* **1997**, *62*, 6424–6428.
17. Martín-Santamaría, S.; Espada, M.; Avendaño, C. *Tetrahedron* **1997**, *53*, 16795–16802.
18. Bartolomé, M. T.; Buenadicha, F. L.; Avendaño, C.; Söllhuber, M. *Tetrahedron: Asymmetry* **1998**, *9*, 249–258.
19. Buenadicha, F.; Bartolomé, M. T.; Aguirre, M. J.; Avendaño, C.; Söllhuber, M. *Tetrahedron: Asymmetry* **1998**, *9*, 483.
20. Fernández, M.; Heredia, M. L.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **1998**, *54*, 2777–2784.
21. Buenadicha, F. L.; Avendaño, C.; Söllhuber, M. *Tetrahedron: Asymmetry* **1998**, *9*, 4275–4284.
22. Martín-Santamaría, S.; Espada, M.; Avendaño, C. *Tetrahedron* **1999**, *55*, 1755–1762.
23. Sánchez, J. D.; Ramos, M. T.; Avendaño, C. *Tetrahedron Lett.* **2000**, *41*, 2745–2748.

24. Karwoski, 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.
25. Chou, T.-C.; Depew, K. M.; Zheng, Y.-H.; Safer, M. L.; Chan, D.; Helfrich, B.; Zatorska, D.; Zatorski, A.; Bornmann, W.; Danishefsky, S. J. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 8369–8374.
26. Mendez-Vidal, C.; Quesada, A. R. *Cancer Lett*. **1998**, *132*, 45–50.
27. Evacuation of oxygen is advisable in radical reactions since nearly all radicals add to triplet oxygen, but given the low reactivity of benzene against radicals [see: *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press, 1991; Vol. 4, p. 720], this unprecedented result was not expected.