Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 1495–1501

Synthesis of enantiopure 4-amino-3-hydroxymethyl-tetrahydroquinolines via an intramolecular nitrone cycloaddition

Gianluigi Broggini,* Francesco Colombo, Ivan De Marchi, Simona Galli, Michela Martinelli and Gaetano Zecchi

Dipartimento di Scienze Chimiche e Ambientali, Università dell'Insubria, via Valleggio 11, 22100 Como, Italy

Received 17 May 2007; accepted 6 June 2007
Available online 5 July 2007

Abstract—Enantiopure 4-amino-3-hydroxymethyl-1,2,3,4-tetrahydroquinolines are synthesized by using an intramolecular cycloaddition of chiral nitrones prepared from aldehydes **5** and (*R*)-α-(hydroxymethyl)benzylhydroxylamine. Reaction times of the nitrone cycloaddition were optimized by activation under MW-assisted conditions. The absolute configuration of the products was determined by X-ray analysis.
© 2007 Elsevier Ltd. All rights reserved.

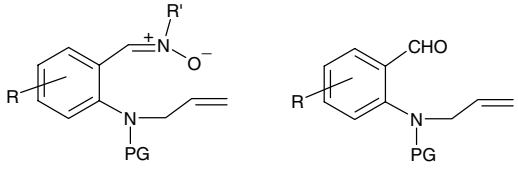
1. Introduction

Nitrones are very useful tools for the construction of structurally complex molecules, in particular nitrogen-containing biologically active compounds.[1] One of the most fruitful synthetic methodologies is represented by 1,3-dipolar nitrone cycloadditions in an intramolecular sense,[2] which allow direct access to fused- or bridged-ring structures, often with a high degree of diastereocontrol. The isoxazolidine derived ring is then susceptible to reductive[3] or oxidative[4] transformations yielding polifunctionalized products.

Considerable effort has been devoted to intramolecular cycloadditions of non-racemic chiral nitrones, above all having a benzylic nature[5] or sugar-derived structure.[6]

1,2,3,4-Tetrahydroquinolines are an important class of compounds among which there are antitumour,[7] cardiovascular,[8] immunosuppressant,[9] NMDA antagonist,[10] antiallergic,[11] antibacterial,[12] analgesic,[13] and antipsychotic[14] agents.

Our synthetic protocol allows access to enantiopure functionalized tetrahydroquinolines by means of the intramolecular cycloaddition of key intermediates of type **A**, bearing a stereocentre at the R′-pendant, available from aldehydes **B**. In turn, we envisaged the possibility of synthesizing intermediates **B** starting from benzoic acids with electron-donor substituents in order to introduce the formyl group under Vilsmeier conditions.



A **B**

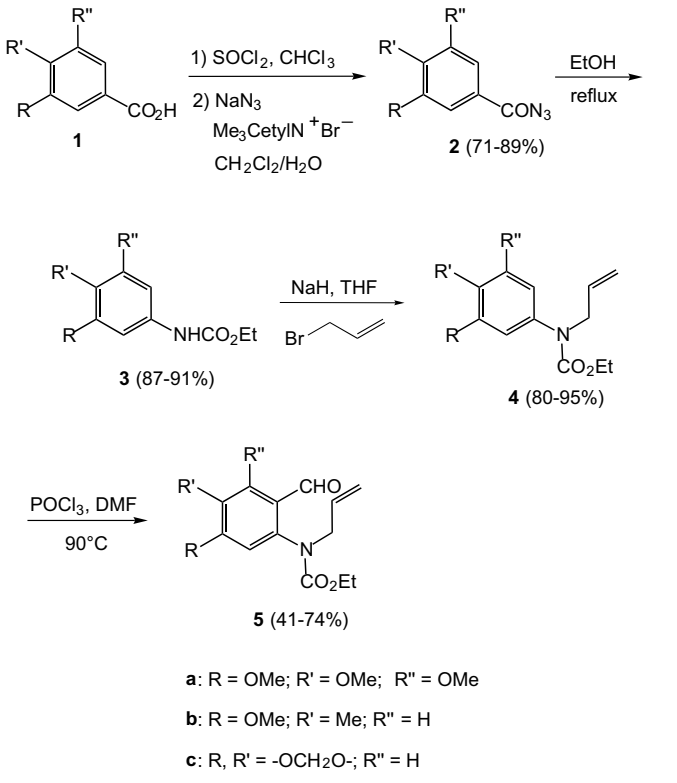
2. Results and discussion

Among the commercially available 4-substituted benzoic acids, 3,4,5-trimethoxy, 3-methoxy-4-methyl, and 3,4-methylenedioxy ones **1a**–**c** were chosen as starting materials for our purpose. As depicted in Scheme 1, compounds **1** were converted in the corresponding acyl azides **2**, which were subsequently refluxed in EtOH to afford carbamates **3** as the product of Curtius degradation. N-Allylation took place in THF with NaH as base giving allylanilines **4**, which were submitted to a Vilsmeier formylation in DMF and $POCl_3$. The latter reaction gave rise to only one isomer in all cases, the attack at the less encumbered *o*-position being most effective.

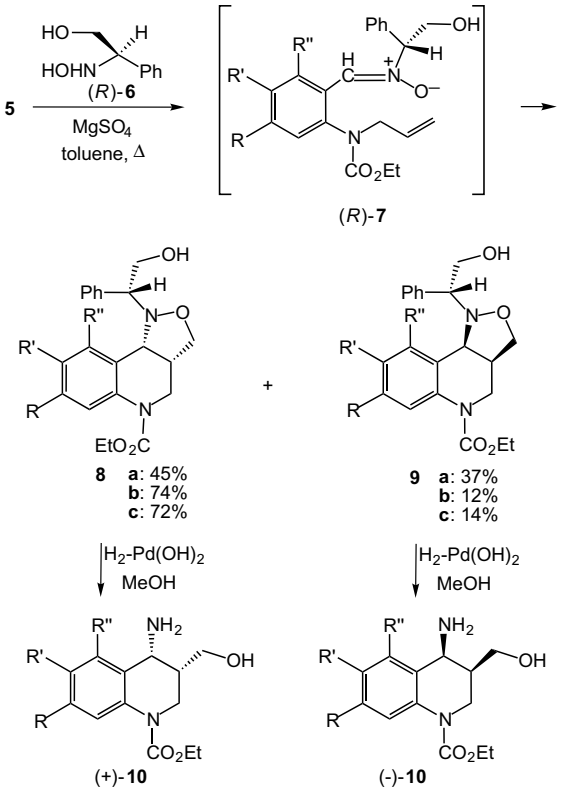
(*R*)-α-(Hydroxymethyl)benzylhydroxylamine, whose synthesis has been reported in the literature,[5d] was chosen as

* Corresponding author. Tel.: +39 031 2386444; fax: +39 031 2386449; e-mail: gianluigi.broggini@uninsubria.it

0957-4166/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2007.06.004



Scheme 1. Synthesis of substituted 2-(*N*-allyl-*N*-carbethoxy-amino)-benzaldehydes **5**.



Scheme 2. Formation and ring opening of cycloadducts **8** and **9**.

the chiral reaction partner of aldehydes **5** in order to generate the non-racemic nitrones (*R*)-**7**. The attempt to generate nitrones **7** failed when the reaction was carried out in diethyl ether at room temperature. However, nitrones (*R*)-**7** were successfully prepared and immediately transformed into cycloadducts in a one-pot reaction by refluxing reactants **5** and (*R*)-**6** in dry toluene for 24 h in the presence of anhydrous $MgSO_4$ (Scheme 2). The resulting crude mixtures contained two products, which were isolated in a pure state by chromatography. Analytical and spectral data are consistent with diastereoisomeric cycloadducts both having a fused-ring skeleton. With the known *R*-configuration of the α-stereocentre, the absolute configuration of the minor product derived from nitrone **7b** (i.e., **9b**) was established to be α*R*,3a*S*,9b*S* by X-ray diffractometric analysis (see Fig. 1). So, the same stereochemistry was reasonably ascribed to the other minor cycloadducts **9a**,**c**.

The regioselective and stereoselective outcome of the cycloaddition deserves some comments. Firstly, the regioselectivity was total being operative only with the approach which binds the nitrone carbon atom to the inner atom of the ethylenic bond. Moreover, all products show a *cis* relationship of the two new stereocentres as a consequence of the intramolecular nature of the reaction, which feels the effect of the strict geometric restraint between dipole and dipolarophile. The induction exerted by the pre-existent stereocentre gave rise to a good diastereoselectivity in the case of nitrones (*R*)-**7b** and (*R*)-**7c** while, unaccountably, no chiral induction was operative in the case of (*R*)-**7a**. As depicted in Figure 2, the intramolecular hydrogen bond

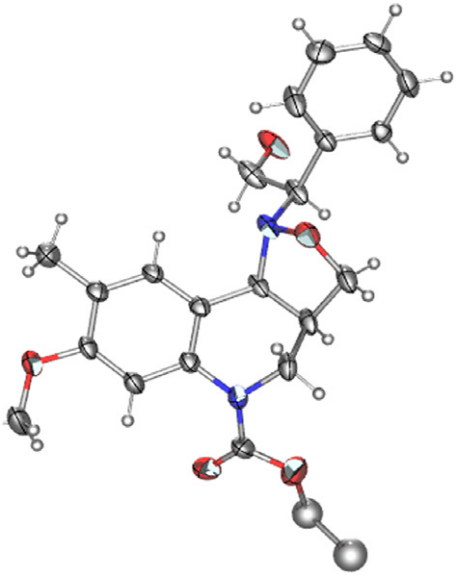


Figure 1. ORTEP plot of **9b**. Atomic displacement parameters at 20% probability level. The CH_2CH_3 residue has been depicted by considering an average ordered model (see Section 4).

of the hydroxyl group with the oxygen atom of the (*Z*)-nitrone determines a chair-like conformation. If the phenyl

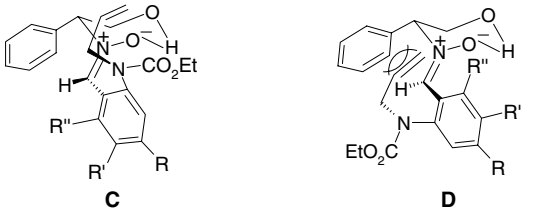


Figure 2. Proposed approach of the functional groups for the formation of compounds **8** and **9**.

group reasonably occupies the equatorial position, the allylic moiety preferably approaches from the upper face (**C**) to avoid steric repulsions.

Since nitrone cycloadditions are ideal candidates for acceleration by microwaves,[15] a series of experiments were carried out under microwave irradiation with the aim of reducing the reaction time. When the mixture of aldehydes **5**, hydroxylamine (*R*)-**6** and $MgSO_4$ in toluene was irradiated at 100 °C in a multimode oven equipped with temperature control at 250 W for 70 min, the cycloaddition process occurred with similar yield and diastereoselective ratio to those obtained by conventional heating.

The last step of our work consisted of the hydrogenolytic treatment of the cycloadducts with the aim of opening the isoxazole ring and removing the benzylic chiral pendant. Compounds **8a**–**c** and **9a**–**c** were submitted to hydrogenation in methanol in the presence of $Pd(OH)_2$ giving both the enantiomers of the 4-amino-3-hydroxymethyl-1,2,3,4-tetrahydroquinolines **10a**–**c**. The enantiomeric purity of the final β-aminoalcohols was confirmed by taking the NMR spectra of compound (+)-**10c** and of its racemate in the presence of (*R*)-*O*-acetylmandelic acid.

3. Conclusion

In conclusion, intramolecular nitrone cycloadditions have been demonstrated to be useful key reactions in the synthesis of highly functionalized 1,2,3,4-tetrahydroquinolines starting from simple 4-substituted benzoic acids.

4. Experimental

4.1. General

Melting points were determined on a Büchi B-540 heating apparatus and are uncorrected. Optical rotations were measured on a Jasco P-1010 polarimeter. ^1H NMR and ^{13}C NMR spectra were obtained on an AVANCE Bruker 400. Chemical shifts are given in parts per million downfield from $SiMe_4$; ^{13}C NMR spectra are ^1H-decoupled and the determination of the multiplicities was achieved by the APT pulse sequence. IR spectra were recorded on a Jasco FT/IR 5300 spectrophotometer. Mass spectra were determined on a WG-70EQ instrument.

4.2. General procedure for the preparation of benzoyl azides 2a–c

These compounds were prepared as described in the literature.[16]

4.2.1. 3-Methoxy-4-methyl-benzoyl azide 2b. Yield: 89%. Mp 104–105 °C (diisopropyl ether). IR (Nujol): 2139, 1687 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.29 (3H, s), 3.90 (3H, s), 7.21 (1H, d, $J = 7.7$ Hz), 7.47 (1H, s), 7.56 (1H, d, $J = 7.7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.0 (q), 55.6 (t), 126.4 (d), 128.2 (d), 132.1 (d), 134.9 (s), 139.1 (s), 143.4 (s), 168.0 (s). MS: *m*/*z* 191 (M^+). Anal. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.74; N, 21.98. Found: C, 56.35; H, 4.91; N, 22.12.

4.3. General procedure for the preparation of *N*-carbethoxybenzenamines 3a–c

A solution of **2a**–**c** (11.7 mmol) in EtOH (20 ml) and toluene (30 ml) was heated at reflux for 24 h. The solvent was removed under reduced pressure to directly give the product.

4.3.1. *N*-Carbethoxy-3,4,5-trimethoxy-benzenamine 3a. Yield: 88%. Mp 88–90 °C (diisopropyl ether). IR (Nujol): 1705 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.32 (3H, t, $J = 7.1$ Hz), 3.82 (3H, s), 3.86 (6H, s), 4.23 (2H, q, $J = 7.1$ Hz), 6.55 (1H, br s, missing after deuteriation), 6.69 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8 (q), 56.2 (q), 56.5 (q), 61.1 (q), 61.2 (t), 96.7 (d), 133.8 (s), 135.0 (s), 153.6 (s), 154.4 (s). MS: *m*/*z* 255 (M^+). Anal. Calcd for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.25; H, 6.99; N, 5.43.

4.3.2. *N*-Carbethoxy-3-methoxy-4-methyl-benzenamine 3b. Yield: 87%. Mp 68–70 °C (diisopropyl ether). IR (Nujol): 1702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.33 (3H, t, $J = 7.1$ Hz), 2.17 (3H, s), 3.84 (3H, s), 4.23 (2H, q, $J = 7.1$ Hz), 6.59 (1H, s), 6.68 (1H, d, $J = 8.0$ Hz), 7.03 (1H, d, $J = 8.0$ Hz), 7.18 (1H, br s, missing after deuteriation); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 16.0 (q), 55.6 (t), 61.4 (t), 102.3 (d), 110.9 (d), 121.7 (s), 130.8 (d), 137.6 (s), 154.5 (s), 158.3 (s). MS: *m*/*z* 209 (M^+). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.01; H, 7.48; N, 6.48.

4.3.3. 5-Carbethoxyamino-benzo[1,3]dioxole 3c. Yield: 91%. Mp 79–81 °C. IR (Nujol): 1704 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.31 (3H, t, $J = 7.1$ Hz), 4.22 (2H, q, $J = 7.1$ Hz), 5.95 (2H, s), 6.56 (1H, s), 6.69 (1H, d, $J = 8.3$ Hz), 6.73 (1H, d, $J = 8.3$ Hz), 7.10 (1H, br s, missing after deuteriation); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 61.6 (t), 101.5 (t), 102.4 (d), 108.4 (d), 112.5 (d), 132.7 (s), 144.1 (s), 148.3 (s), 154.4 (s). MS: *m*/*z* 209 (M^+). Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.18; H, 5.49; N, 6.92.

4.4. General procedure for the preparation of *N*-allyl-*N*-carbethoxy-benzenamines 4a–c

NaH (155 mg, 6.46 mmol) was added in an N_2 atmosphere to a solution of **3a–c** (4.31 mmol) in dry THF (50 ml). Allyl bromide (1.04 g, 8.62 mmol) was added at −3 °C, and then the mixture was refluxed for 24 h. After cooling at room temperature, H_2O was added. The mixture was extracted with CH_2Cl_2 (2 × 60 ml), and the organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude products were purified through a silica gel column with light petroleum/AcOEt = 10/1 as eluent.

4.4.1. *N*-Allyl-*N*-carbethoxy-3,4,5-trimethoxy-benzenamine 4a. Yield: 95%. Oil. IR (Nujol): 1703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.24 (3H, t, $J = 7.0$ Hz), 3.81 (6H, s), 3.83 (3H, s), 4.17 (2H, q, $J = 7.0$ Hz), 4.21 (2H, d, $J = 5.8$ Hz), 5.15 (1H, dd, $J = 1.4$, 17.2 Hz), 5.17 (1H, dd, $J = 1.4$, 10.2 Hz), 5.93 (1H, tdd, $J = 5.8$, 10.2, 17.2 Hz), 6.46 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 53.8 (t), 56.4 (q), 56.5 (q), 61.1 (q), 62.0 (t), 104.7 (d), 104.8 (d), 117.3 (t), 134.5 (d), 136.8 (s), 138.4 (s), 153.3 (s), 153.4 (s), 155.8 (s). MS: *m/z* 295 (M^+). Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.79; H, 7.28; N, 4.96.

4.4.2. *N*-Allyl-*N*-carbethoxy-3-methoxy-4-methyl-benzenamine 4b. Yield: 80%. Oil. IR (Nujol): 1707 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.25 (3H, t, $J = 6.9$ Hz), 2.21 (3H, s), 3.81 (3H, s), 4.19 (2H, q, $J = 6.9$ Hz), 4.26 (2H, d, $J = 5.8$ Hz), 5.15 (1H, dd, $J = 0.7$, 10.0 Hz), 5.18 (1H, dd, $J = 0.7$, 17.2 Hz), 5.95 (1H, tdd, $J = 5.8$, 10.0, 17.2 Hz), 6.72–6.74 (2H, overlapping), 7.08 (1H, d, $J = 8.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 16.1 (q), 55.6 (t), 55.4 (d), 61.8 (t), 109.4 (d), 117.1 (t), 118.6 (d), 125.0 (s), 130.6 (d), 134.6 (d), 141.5 (s), 155.7 (s), 158.0 (s). MS: *m/z* 249 (M^+). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.42; H, 7.94; N, 5.47.

4.4.3. 5-(*N*-Allyl-*N*-carbethoxy-amino)-benzo[1,3]dioxole 4c. Yield: 86%. Oil. IR (Nujol): 1703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.23 (3H, t, $J = 7.0$ Hz), 4.16 (2H, q, $J = 7.0$ Hz), 4.19 (2H, d, $J = 5.9$ Hz), 5.13 (1H, d, $J = 16.4$ Hz), 5.15 (1H, d, $J = 11.3$ Hz), 5.95 (1H, ddd, $J = 5.9$, 11.3, 16.4 Hz), 5.98 (2H, s), 6.65–6.71 (2H, overlapping), 6.76 (1H, d, $J = 8.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.5 (q), 53.7 (t), 61.8 (t), 101.7 (t), 108.1 (d), 108.8 (d), 117.3 (t), 120.5 (d), 134.2 (d), 136.4 (s), 146.3 (s), 148.0 (s), 155.7 (s). MS: *m/z* 249 (M^+). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.74; H, 5.79; N, 5.43.

4.5. General procedure for the preparation of 2-formyl-*N*-allyl-*N*-carbethoxy-benzenamines 5a–c

A solution of $POCl_3$ (6.3 g, 0.041 mol) in DMF (9.5 ml) was stirred at 0 °C for 1 h under N_2. After the addition of a solution of **4a–c** (0.013 mol) in 2 ml $CHCl_3$, the mixture was warmed at 90 °C for 48 h. The mixture was adjusted to pH 8 with $NaHCO_3$, then vigorously stirred for 1 h and extracted with CH_2Cl_2 (2 × 250 ml). The organic layer was dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude products were purified through a silica gel column.

4.5.1. *N*-Allyl-*N*-carbethoxy-2-formyl-3,4,5-trimethoxy-benzenamine 5a. Eluent: light petroleum/AcOEt = 3/1. Yield: 74%. Mp 58–60 °C (diisopropyl ether). IR (Nujol): 1715, 1663 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.09 (3H, br s), 3.89 (6H, s), 3.99 (3H, s), 4.03–4.20 (3H, overlapping), 4.43 (1H, br s), 5.08 (1H, dd, $J = 1.4$, 10.2 Hz), 5.12 (1H, dd, $J = 1.4$, 17.2 Hz), 5.90 (1H, tdd, $J = 5.9$, 10.2, 17.2 Hz), 6.51 (1H, s), 10.20 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8 (q), 53.8 (t), 56.5 (q), 61.2 (q), 61.9 (t), 62.7 (q), 109.2 (d), 117.9 (t), 119.9 (s), 134.2 (d), 138.7 (s), 141.3 (s), 155.5 (s) 157.6 (s), 158.3 (s), 188.3 (d). MS: *m/z* 323 (M^+). Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.58; H, 6.30; N, 4.11.

4.5.2. *N*-Allyl-*N*-carbethoxy-2-formyl-5-methoxy-4-methyl-benzenamine 5b. Eluent: light petroleum/AcOEt = 5/1. Yield: 48%. Oil. IR (Nujol): 1718, 1667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.12 (3H, t, $J = 7.1$ Hz), 2.24 (3H, s), 3.89 (3H, s), 4.18 (2H, q, $J = 7.1$ Hz), 4.24 (2H, d, $J = 5.9$ Hz), 5.12 (1H, d, $J = 16.1$ Hz), 5.16 (1H, d, $J = 9.0$ Hz), 5.95 (1H, tdd, $J = 5.9$, 9.0, 16.1 Hz), 6.64 (1H, s), 7.69 (1H, s), 9.93 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8 (q), 16.0 (q), 54.3 (t), 56.1 (q), 62.3 (t), 106.3 (d), 117.7 (t), 125.8 (s), 126.9 (s), 131.3 (d), 133.4 (d), 144.2 (s), 155.7 (s) 163.1 (s), 189.0 (d). MS: *m/z* 277 (M^+). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.13; H, 6.66; N, 5.16.

4.5.3. 5-(*N*-Allyl-*N*-carbethoxy-amino)-6-formyl-benzo-[1,3]dioxole 5c. Eluent: light petroleum/AcOEt = 1/1. Yield: 41%. Oil. IR (Nujol): 1714, 1662 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.16 (3H, t, $J = 7.1$ Hz), 4.06–4.22 (4H, overlapping), 5.10 (1H, d, $J = 17.4$ Hz), 5.14 (1H, d, $J = 11.3$ Hz), 5.95 (1H, tdd, $J = 6.7$, 11.3, 17.4 Hz), 6.06 (2H, s), 6.65 (1H, s), 7.29 (1H, s), 9.86 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8 (q), 54.4 (t), 62.4 (t), 101.5 (t), 103.0 (t), 106.8 (d), 107.1 (d), 117.6 (s), 119.5 (s), 128.0 (s), 132.9 (d), 147.8 (s), 157.3 (s), 188.4 (d). MS: *m/z* 277 (M^+). Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.65; H, 5.45; N, 5.05. Found: C, 60.87; H, 5.41; N, 4.82.

4.6. General procedure for the reactions of 5a–c with (*R*)-6

Hydroxylamine (*R*)-**6** (0.380 g, 2.48 mmol) and $MgSO_4$ (2.60 g, 21.7 mmol) were added to a solution of **5a–c** (2.16 mmol) in toluene (70 ml). The mixture was warmed at 100 °C for 24 h and then, after cooling to room temperature, filtered on Celite. The solvent was removed under reduced pressure and the crude residue was purified through a silica gel column.

Entry a: Elution with AcOEt/light petroleum (6:4) gave **8a** (45%) and **9a** (37%).

4.6.1. (αR,3aR,9bR)-5-Carbethoxy-1-(1-phenyl-2-hydroxyethyl)-7,8,9-trimethoxy-1,3a,4,9b-tetrahydro-3H-isoxazolo[4,3-c]quinoline 8a. IR (Nujol): 3478, 1701 cm^{-1}. Mp 49–51 °C (diisopropyl ether). $[\alpha]_D^{23} = -19.5$ (*c* 0.7, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.30 (3H, t, $J = 7.1$ Hz), 2.09 (1H, br s, missing after deuteriation), 2.89–2.95 (1H, m), 3.06 (1H, dd, $J = 3.3$, 13.4 Hz), 3.65 (1H, dd, $J = 1.7$, 8.5 Hz), 3.76 (1H, dd, $J = 7.2$, 8.2 Hz), 3.86 (3H, s), 3.92 (3H, s), 3.96 (3H, s), 4.01–4.08 (3H, overlapping), 4.19 (1H, dd, $J = 7.1$, 17.8 Hz), 4.30 (1H, dd, $J = 7.1$, 17.8 Hz), 4.32 (1H, dd, $J = 7.8$, 13.4 Hz), 4.51 (1H, d, $J = 9.3$ Hz), 6.91 (1H, s), 7.33–7.38 (3H, overlapping), 7.52–7.55 (2H, overlapping); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 44.3 (d), 46.4 (t), 56.3 (q), 57.4 (d), 61.3 (q), 61.5 (q), 62.5 (t), 64.5 (t), 68.6 (d), 69.6 (t), 104.9 (d), 115.8 (s) 128.3 (d), 128.4 (d), 130.5 (d), 136.8 (s), 137.1 (s), 139.5 (s), 152.5 (s), 153.1 (s), 156.9 (s). MS: *m*/*z* 458 (M^+). Anal. Calcd for $C_{24}H_{30}N_2O_7$: C, 62.87; H, 6.59; N, 6.11. Found: C, 63.13; H, 6.30; N, 6.22.

4.6.2. (αR,3aS,9bS)-5-Carbethoxy-1-(1-phenyl-2-hydroxyethyl)-7,8,9-trimethoxy-1,3a,4,9b-tetrahydro-3H-isoxazolo[4,3-c]quinoline 9a. IR (Nujol): 3489, 1702 cm^{-1}. Mp 46–48 °C (diisopropyl ether). $[\alpha]_D^{23} = -63.5$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.34 (3H, t, $J = 7.1$ Hz), 3.01 (1H, br s, missing after deuteriation), 3.06 (1H, dd, $J =$ 2.2, 13.3 Hz), 3.23–2.26 (1H, m), 3.44 (3H, s), 3.74 (3H, s), 3.76–3.82 (4H, overlapping), 3.99 (1H, dd, $J = 5.4$, 8.4 Hz), 4.04 (1H, dd, $J = 3.2$, 6.7 Hz), 4.09–4.14 (1H, m), 4.23 (1H, dd, $J = 7.1$, 10.6 Hz), 4.34 (1H, dd, $J = 7.1$, 10.6 Hz), 4.41–4.49 (3H, overlapping), 6.84 (1H, s), 7.28–7.33 (3H, overlapping), 7.37–7.40 (2H, overlapping); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 43.4 (d), 46.7 (t), 56.3 (q), 60.0 (d), 60.4 (q), 61.1 (q), 62.5 (t), 67.2 (t), 69.4 (d), 69.6 (t), 103.9 (d), 115.7 (s), 128.1 (d), 128.5 (d), 129.4 (d), 136.7 (s), 138.3 (s), 139.0 (s), 152.5 (s), 152.9 (s), 155.7 (s). MS: *m*/*z* 458 (M^+). Anal. Calcd for $C_{24}H_{30}N_2O_7$: C, 62.87; H, 6.59; N, 6.11. Found: C, 62.79; H, 5.91; N, 6.38.

Entry b: Elution with AcOEt/light petroleum (1:1) gave **9b** (12%) and **8b** (74%).

4.6.3. (αR,3aR,9bR)-5-Carbethoxy-1-(1-phenyl-2-hydroxyethyl)-7-methoxy-8-methyl-1,3a,4,9b-tetrahydro-3H-isoxazolo[4,3-c]quinoline 8b. IR (Nujol): 3481, 1701 cm^{-1}. Mp 56–58 °C (diisopropyl ether). $[\alpha]_D^{23} = -11.1$ (*c* 0.9, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.33 (3H, t, $J = 7.1$ Hz), 2.07 (3H, s), 3.04 (1H, br s, missing after deuteriation), 3.31–3.38 (1H, m), 3.43 (1H, dd, $J = 3.5$, 13.4 Hz), 3.77–3.80 (4H, overlapping), 3.98 (1H, dd, $J = 4.9$, 8.5 Hz), 4.05 (1H, dd, $J = 3.2$, 6.9 Hz), 4.14–4.18 (2H, overlapping), 4.23–4.30 (3H, overlapping), 4.48 (1H, dd, $J = 8.4$, 8.5 Hz), 6.67 (1H, s), 7.02 (1H, s), 7.36–7.45 (5H, overlapping); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 16.2 (q), 42.5 (d), 46.1 (t), 55.8 (q), 62.4 (t), 63.6 (d), 68.0 (t), 69.5 (t), 69.7 (d), 106.0 (d), 120.9 (s), 123.8 (s) 128.9 (d), 129.1 (d), 129.3 (d), 131.6 (d), 138.3 (s), 138.8 (s) 155.1 (s), 156.9 (s). MS: *m*/*z* 412 (M^+). Anal. Calcd for $C_{23}H_{28}N_2O_5$: C, 66.97; H, 6.84; N, 6.79. Found: C, 67.25; H, 7.14; N, 6.57.

4.6.4. (αR,3aS,9bS)-5-Carbethoxy-1-(1-phenyl-2-hydroxyethyl)-7-methoxy-8-methyl-1,3a,4,9b-tetrahydro-3H-isoxazolo[4,3-c]quinoline 9b. IR (Nujol): 3472, 1700 cm^{-1}. Mp 172–174 °C (diisopropyl ether). $[\alpha]_D^{23} = -9.3$ (*c* 0.8, $CHCl_3$). ^1H NMR (400 MHz, 50 °C, $CDCl_3$) δ: 1.32 (3H, t, $J = 7.1$ Hz), 2.25 (3H, s), 2.55 (1H, br s, missing after deuteriation), 2.88–2.92 (1H, m), 3.19 (1H, dd, $J = 4.9$, 13.5 Hz), 3.63 (1H, ddd, $J = 4.7$, 9.2, 9.9 Hz), 3.82 (1H, d, $J = 8.3$ Hz), 3.85 (3H, s), 3.91 (1H, d, $J = 8.7$ Hz), 3.93 (1H, dd, $J = 4.7$, 9.3 Hz), 4.05 (1H, dd, $J = 9.3$, 9.9 Hz), 4.12 (1H, d, $J = 8.3$ Hz), 4.17 (1H, dd, $J = 2.5$, 13.5 Hz), 4.25 (1H, dq, $J = 7.1$, 10.7 Hz), 4.33 (1H, dq, $J = 7.1$, 10.7 Hz), 6.94 (1H, s), 7.06 (1H, s), 7.36–7.42 (3H, overlapping), 7.46–7.49 (2H, overlapping); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.0 (q), 16.4 (q), 45.8 (d), 46.9 (t), 55.8 (q), 60.6 (d), 62.4 (t), 64.1 (t), 67.3 (d), 70.1 (t), 107.7 (d), 120.2 (s), 124.0 (s) 128.5 (d), 128.7 (d), 130.8 (d), 131.8 (d), 136.0 (s), 139.9 (s), 155.5 (s), 157.7 (s). MS: *m*/*z* 412 (M^+). Anal. Calcd for $C_{23}H_{28}N_2O_5$: C, 66.97; H, 6.84; N, 6.79. Found: C, 67.13; H, 6.55; N, 6.99.

Entry c: Elution with AcOEt/light petroleum (1:2) gave **9c** (14%) and **8c** (72%).

4.6.5. (αR,3aR,10bR)-5-Carbethoxy-1-(1-phenyl-2-hydroxyethyl)-1,3a,4,10b-tetrahydro-3H,8H-[1,3]dioxolo[4,5-g]isoxazolo[4,3-c]quinoline 8c. IR (Nujol): 3492, 1705 cm^{-1}. Mp 198–200 °C. $[\alpha]_D^{23} = -7.9$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.31 (3H, t, $J = 7.0$ Hz), 2.95 (1H, br s, missing after deuteriation), 3.34–3.39 (1H, m), 3.48 (1H, dd, $J = 3.6$, 13.4 Hz), 3.78 (1H, d, $J = 6.7$, Hz), 3.95 (1H, dd, $J = 4.8$, 8.5 Hz), 4.03 (1H, dd, $J = 3.5$, 6.7 Hz), 4.13–4.17 (2H, overlapping), 4.25 (2H, q, $J = 7.0$ Hz), 4.49 (1H, dd, $J = 8.3$, 8.5 Hz), 4.56 (1H, dd, $J = 8.3$, 8.5 Hz), 5.89 (2H, s), 6.42 (1H, s), 6.94 (1H, s), 7.35–7.43 (5H, overlapping); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 42.7 (d), 46.4 (t), 62.5 (t), 64.1 (d), 67.9 (t), 69.5 (d), 69.7 (t), 101.5 (t), 105.3 (d), 108.7 (d), 123.0 (s) 128.9 (d), 129.0 (d), 129.4 (d), 133.9 (s), 138.7 (s), 145.0 (s) 146.9 (s), 155.1 (s). MS: *m*/*z* 412 (M^+). Anal. Calcd for $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79. Found: C, 64.30; H, 5.61; N, 6.55.

4.6.6. (αR,3aS,10bS)-5-Carbethoxy-1-(1-phenyl-2-hydroxyethyl)-1,3a,4,10b-tetrahydro-3H,8H-[1,3]dioxolo[4,5-g]isoxazolo[4,3-c]quinoline 9c. IR (Nujol): 3475, 1705 cm^{-1}. Mp 136–138 °C (diisopropyl ether). $[\alpha]_D^{23} = -7.4$ (*c* 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.32 (3H, t, $J = 7.1$ Hz), 2.49 (1H, br s, missing after deuteriation), 2.90–2.94 (1H, m), 3.13 (1H, dd, $J = 5.1$, 13.5 Hz), 3.63 (1H, dd, $J = 4.7$, 10.5 Hz), 3.82 (1H, d, $J = 8.0$ Hz), 3.87 (1H, d, $J = 8.9$ Hz), 3.92 (1H, dd, $J = 4.7$, 9.9 Hz), 4.06 (1H, dd, $J = 9.9$, 10.5 Hz), 4.14 (1H, dd, $J = 8.4$, 8.9 Hz), 4.16 (1H, dd, $J = 2.2$, 13.5 Hz), 4.25 (1H, dq, $J = 7.1$, 10.0 Hz), 4.29 (1H, dq, $J = 7.1$, 10.0 Hz), 5.99 (2H, s), 6.68 (1H, s), 6.99 (1H, s), 7.35–7.41 (3H, overlapping), 7.45–7.48 (2H, overlapping); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.0 (q), 46.2 (d), 47.3 (t), 61.4 (d), 62.5 (t), 64.0 (t), 67.3 (d), 70.2 (t), 101.9 (t), 107.3 (d), 109.4 (d), 122.1 (s) 128.6 (d), 128.7 (d), 130.7 (d), 135.6 (s), 135.7 (s), 145.4 (s) 147.8 (s), 155.6 (s). MS: *m*/*z* 412 (M^+). Anal. Calcd for

$C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79. Found: C, 63.99; H, 6.16; N, 6.49.

4.7. General procedure for the reactions of 5a–c with (*R*)-6 under microwave irradiation

A suspension of hydroxylamine (*R*)-**6** (0.30 g, 1.98 mmol), $MgSO_4$ (2.08 g, 17.4 mmol) and **5a**–**c** (1.73 mmol) in toluene (70 ml) was heated in a microwave oven (250 W) at 100 °C for 70 min. The mixture was filtered on Celite and the solvent was removed under reduced pressure after which the crude residue was purified through a silica gel column (eluent given before) to give compounds **8a**–**c** and **9a**–**c**.

4.8. General procedure for the hydrogenation of compounds 8a–c and 9a–c

A suspension of 20% $Pd(OH)_2/C$ (120 mg, 0.17 mmol) and isoxazolidine derived compound **8a**–**c** or **9a**–**c** (0.33 mmol) in MeOH (12 ml) was stirred under H_2 for 24 h. The mixture was filtered through a Celite path and the solvent was removed under reduced pressure after which the crude residue was purified through a silica gel column to give enantiopure 1,3-aminoalcohol **10a**–**c**.

4.8.1. (3*R*,4*R*)-4-Amino-1-carbethoxy-3-hydroxymethyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroquinoline 10a. IR (Nujol): 3371, 3298, 1753 cm^{-1}. Yield: 81%. Oil. $[\alpha]_D^{23} = +23.3$ (*c* 1.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.28 (3H, t, $J = 7.0$ Hz), 1.94–1.98 (1H, m), 3.12 (3H, br s, missing after deuteriation), 3.57 (1H, dd, $J = 12.7$, 13.1 Hz), 3.81–3.89 (7H, overlapping), 3.97 (3H, s), 4.08 (1H, dd, $J = 3.1$, 10.7 Hz), 4.18 (1H, dd, $J = 2.9$, 13.1 Hz), 4.26 (2H, q, $J = 7.0$ Hz), 4.32 (1H, d, $J = 4.0$ Hz), 7.44 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 39.2 (d), 42.6 (t), 46.7 (d), 56.3 (d), 61.2 (q), 61.7 (q), 62.5 (t), 64.1 (t), 103.0 (d), 118.7 (s), 133.1 (s), 138.2 (s), 150.7 (s), 152.9 (s), 155.1 (s). MS: *m*/*z* 340 (M^+). Anal. Calcd for $C_{16}H_{24}N_2O_6$: C, 56.46; H, 7.11; N, 8.23. Found: C, 56.31; H, 7.28; N, 7.97.

4.8.2. (3*S*,4*S*)-4-Amino-1-carbethoxy-3-hydroxymethyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroquinoline 10a. Yield: 79%. $[\alpha]_D^{23} = -22.9$ (*c* 1.1, $CHCl_3$)

4.8.3. (3*R*,4*R*)-4-Amino-1-carbethoxy-3-hydroxymethyl-7-methoxy-6-methyl-1,2,3,4-tetrahydroquinoline 10b. IR (Nujol): 3371, 3293, 1707 cm^{-1}. Yield: 74%. Oil. $[\alpha]_D^{23} = +29.3$ (*c* 0.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.35 (3H, t, $J = 7.1$ Hz), 2.04–2.09 (1H, m), 2.17 (3H, s), 3.40 (3H, br s, missing after deuteriation), 3.65 (1H, dd, $J = 12.2$, 13.1 Hz), 3.78 (1H, dd, $J = 5.7$, 11.5 Hz), 3.82 (3H, s), 3.95 (1H, dd, $J = 3.1$, 11.5 Hz), 4.04 (1H, dd, $J = 4.9$, 13.1 Hz), 4.07 (1H, d, $J = 4.7$ Hz), 4.26 (2H, q, $J = 7.1$ Hz), 6.97 (1H, s) 7.52 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 15.9 (q), 39.7 (d), 42.8 (t), 50.6 (d), 55.8 (q), 62.4 (t), 63.1 (t), 105.6 (d), 122.6 (s), 123.8 (s), 130.0 (d), 136.8 (s), 155.1 (s), 157.3 (s). MS: *m*/*z* 294 (M^+). Anal. Calcd for $C_{15}H_{22}N_2O_4$: C, 61.21; H, 7.53; N, 9.52. Found: C, 61.25; H, 7.38; N, 9.81.

4.8.4. (3*S*,4*S*)-4-Amino-1-carbethoxy-3-hydroxymethyl-7-methoxy-6-methyl-1,2,3,4-tetrahydroquinoline 10b. Yield: 71%. $[\alpha]_D^{23} = -29.9$ (*c* 0.5, $CHCl_3$).

4.8.5. (7*R*,8*R*)-8-Amino-5-carbethoxy-7-hydroxymethyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,3-*c*]quinoline 10c. IR (Nujol): 3377, 3296, 1703 cm^{-1}. Yield: 78%. Oil. $[\alpha]_D^{23} = +25.9$ (*c* 0.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.31 (3H, t, $J = 7.1$ Hz), 2.03–2.08 (1H, m), 3.25 (3H, br s, missing after deuteriation), 3.64 (1H, dd, $J = 11.1$, 12.6 Hz), 3.77 (1H, dd, $J = 5.4$, 11.3 Hz), 3.93 (1H, dd, $J = 5.4$, 11.3 Hz), 3.96–4.01 (2H, overlapping), 4.25 (2H, q, $J = 7.1$ Hz), 5.93 (2H, s), 6.67 (1H, s), 7.34 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 39.9 (d), 42.9 (t), 51.4 (d), 62.4 (t), 62.6 (t), 101.7 (t), 105.5 (d), 107.6 (d), 124.3 (s), 131.6 (s), 144.2 (s), 147.6 (s), 155.2 (s). MS: *m*/*z* 294 (M^+). Anal. Calcd for $C_{14}H_{18}N_2O_5$: C, 57.14; H, 6.16; N, 9.52. Found: C, 56.92; H, 6.34; N, 9.62.

4.8.6. (7*S*,8*S*)-8-Amino-5-carbethoxy-7-hydroxymethyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,3-*c*]quinoline 10c. IR (Nujol): 3377, 3296, 1703 cm^{-1}. Yield: 74%. Oil. $[\alpha]_D^{23} = -25.1$ (*c* 0.5, $CHCl_3$).

4.8.7. X-ray crystallography for 9b. Monoclinic, space group *C*2, $a = 35.22(3)$, $b = 5.008(6)$, $c = 12.10(1)$ Å, $\beta = 96.59(8)°$, $V = 2121(4)$ $Å^3$, $Z = 4$, $F(000) = 880$, $\rho = 1.292$ g cm^{-3}, μ(Mo Kα) = 0.091 mm^{-1}. The *R*, *wR* figures of merit reached final values of 0.078, 0.181 for the 1981 observed reflections, and 0.157, 0.226 for all of the unique reflections, 269 parameters and 7 restraints. Goodness of fit, highest peak and deepest hole reached final values of 1.014, 0.252 e $Å^{-3}$ and −0.198 e $Å^{-3}$.

A needle colourless crystal of approximate $0.02 \times 0.02 \times 0.16$ mm dimensions was mounted on top of a goniometer head. The data were collected on a Enraf Nonius CAD-4 automated diffractometer using graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). The unit cell was determined on the basis of the setting angles of 25 randomly distributed reflections in the $8.0° < \theta < 11.5°$ range. A total of 3945 unique and 1981 observed [$I > 2\sigma(I)$] reflections, in the $3.0° < \theta < 25.3°$ range, were collected by applying the ω-scan mode [$\Delta\omega = 1.2 + (0.35 \tan\theta)$]. The data were corrected for Lorenz polarization. No absorption corrections were applied. The structure was solved by direct methods and refined by full-matrix least-squares on F^2. All the ordered non-hydrogen atoms were refined anisotropically. Hydrogen atoms were made riding their parent atoms with an isotropic temperature factor 1.2 times that of their parent atoms. A $-CH_2CH_3$ moiety, affected by disorder, was modelled by superimposing two, geometrically identical, C–C vectors, restraining the C–C and O–C distances to 1.54 and 1.48 Å, respectively, and assigning to each C atom a s.o.f. of 0.5. No hydrogen atoms were introduced on the carbon atoms of the disordered part and on the –OH groups. CCDC Number 646199.

Acknowledgements

We are grateful to MIUR for financial support and to the Centro Interuniversitario di Ricerca sulle Reazioni Pericicliche e Sintesi di Sistemi Etero e Carbociclici.

References

1. Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: New York, 1988.
2. (a) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1–173; (b) Chiacchio, U.; Rescifina, A.; Romeo, G. In *Targets in Heterocyclic Systems*; Attanasi, O. A., Spinelli, D., Eds.; SCI: Rome, 1997; Vol. I, pp 225–276; (c) Frederickson, M. *Tetrahedron* **1997**, *53*, 403–425; (d) Beccalli, E. M.; Broggini, G.; Contini, A.; De Marchi, I.; Zecchi, G.; Zoni, C. *Tetrahedron: Asymmetry* **2004**, *15*, 3181–3187; (e) Padwa, A.; Pearson, W. H. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Wiley: New York, 2003, Chapter 1; (f) Jeong, J. H.; Weinreb, S. M. *Org. Lett.* **2006**, *8*, 2309–2312; (g) Gravestock, M. B.; Knight, D. W.; Lovell, J. S.; Thornton, S. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3143–3155; (h) Werner, K. M.; De los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 4865–4873; (i) Romeo, R.; Iannazzo, D.; Piperno, A.; Chiacchio, M. A.; Corsaro, A.; Rescifina, A. *Eur. J. Org. Chem.* **2005**, 2368–2373; (j) Alcaide, B.; Saez, E. *Eur. J. Org. Chem.* **2005**, 1680–1693; (k) Aggarwal, V. K.; Roseblade, S.; Alexander, R. *Org. Biomol. Chem.* **2003**, *1*, 684–691; (l) Cordero, F. M.; Pisaneschi, F.; Gensini, M.; Goti, A.; Brandi, A. *Eur. J. Org. Chem.* **2002**, 1941–1951; (m) Davison, E. C.; Fox, M. E.; Holmes, A. B.; Roughley, S. D.; Smith, C. J.; Williams, G. M.; Davies, J. E.; Raithby, P. R.; Adams, J. P.; Forbes, I. T.; Press, N. J.; Thompson, M. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1494–1514.
3. (a) Nath, M.; Mukhopadhyay, R.; Bhattacharjya, A. *Org. Lett.* **2006**, *9*, 317–320; (b) Revuelta, J.; Cicchi, S.; Brandi, A. *J. Org. Chem.* **2005**, *70*, 5636–5642; (c) Basso, D.; Broggini, G.; Passarella, D.; Pilati, T.; Terraneo, A.; Zecchi, G. *Tetrahedron* **2002**, *58*, 4445–4450; (d) Casuscelli, F.; Chiacchio, U.; Di Bella, M. R.; Rescifina, A.; Romeo, G.; Romeo, R.; Uccella, N. *Tetrahedron* **1995**, *51*, 8605–8612; (e) Funk, R. L.; Bolton, G. L. *J. Org. Chem.* **1984**, *49*, 5021–5022; (f) Liautard, V.; Christina, A. E.; Desvergnes, V.; Martin, O. R. *J. Org. Chem.* **2006**, *71*, 7337–7345; (g) Tufariello, J.; Dyszlewski, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1138–1140; (h) Alvarez de Cienfuegos, L.; Langlois, N. *Tetrahedron: Asymmetry* **2006**, *17*, 1863–1866; (i) Alibés, R.; Blanco, P.; Casas, P.; Montserrat, C.; de March, P.; Figueredo, M.; Font, J.; Sanfeliu, E.; Alvarez-Larena *J. Org. Chem.* **2005**, *70*, 3157–3167.
4. (a) Broggini, G.; De Marchi, I.; Martinelli, M.; Zecchi, G. In *Targets in Heterocyclic Systems*; Attanasi, O. A., Spinelli, D., Eds.; SCI: Rome, 2005; Vol. 9, pp 211–229; (b) Wang, P.-F.; Gao, P.; Xu, P.-F. *Synlett* **2006**, 1095–1099.
5. (a) Broggini, G.; Chiesa, K.; De Marchi, I.; Martinelli, M.; Pilati, T.; Zecchi, G. *Tetrahedron* **2005**, *61*, 3525–3531; (b) Hanselmann, R.; Zhou, J.; Ma, P.; Confalone, P. A. *J. Org. Chem.* **2003**, *68*, 8739–8741; (c) Zhao, Q.; Han, F.; Romero, D. L. *J. Org. Chem.* **2002**, *67*, 8669–8672; (d) Tamura, O.; Gotanda, K.; Yoshino, J.; Morita, Y.; Terashima, R.; Kikuchi, M.; Miyawaki, T.; Mita, N.; Yamashita, M.; Ishibashi, H.; Sakamoto, M. *J. Org. Chem.* **2000**, *65*, 8544–8551; (e) Beccalli, E. M.; Broggini, G.; La Rosa, C.; Passarella, D.; Pilati, T.; Terraneo, A.; Zecchi, G. *J. Org. Chem.* **2000**, *65*, 8924–8932; (f) Arnone, A.; Broggini, G.; Passarella, D.; Terraneo, A.; Zecchi, G. *J. Org. Chem.* **1998**, *63*, 9279–9284; (g) Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron* **1985**, *41*, 3455–3462.
6. (a) Osborn, H. M. I.; Gemmell, N.; Harwood, L. M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2419–2438; (b) Shing, T. K. M.; Wong, W. F.; Ikeno, T.; Yamada, T. *Org. Lett.* **2007**, *9*, 207–209; (c) Pádár, P.; Bokros, A.; Paragi, G.; Forgó, P.; Kele, Z.; Howarth, N. M.; Kovács, L. *J. Org. Chem.* **2006**, *71*, 8669–8672; (d) Moutel, S.; Shipman, M.; Martin, O. R.; Ikeda, K.; Asano, N. *Tetrahedron: Asymmetry* **2005**, *16*, 487–491; (e) Sahabuddin, Sk.; Roy, A.; Drew, M. G. B.; Roy, B. G.; Achari, B.; Mandal, S. B. *J. Org. Chem.* **2006**, *71*, 5980–5992; (f) Shing, T. K. M.; Wong, W. F.; Ikeno, T.; Yamada, T. *J. Org. Chem.* **2006**, *71*, 3253–3263; (g) Sharma, G. V. M.; Begum, A.; Reddy, K. R.; Sankar, A. R.; Kunwar, A. C. *Tetrahedron: Asymmetry* **2003**, *14*, 3899–3905; (h) Bhattacharjee, A.; Datta, S.; Chattopadhyay, P.; Ghoshal, N.; Kundu, A. P.; Pal, A.; Mukhopadhyay, R.; Chowdhury, S.; Bhattacharjya, A.; Patra, A. *Tetrahedron* **2003**, *59*, 4623–4639.
7. (a) Ganton, M. D.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 574–582; (b) Schiemann, K.; Bruge, D.; Buchstaller, H.-P.; Emde, U.; Finsinger, D.; Amendt, C.; Zenke, F. Ger. Offen. 61214, 2006; *Chem. Abstr.* **2007**, *146*, 62604; (c) Li, C.-J.; Zhang, J. U.S. Patent Appl. Publ. 149069, 2003; *Chem. Abstr.* **2003**, *139*, 164711; (d) Searcey, M.; Patterson, L. H. PCT Int. Appl. 67937, 2002; *Chem. Abstr.* **2002**, *137*, 216884.
8. (a) Eda, M.; Takemoto, H.; Hihara, M.; Sakashita, H.; Okada, T.; Eiraku, M.; Fukaya, T.; Nakamura, N.; Matsuno, S. Jpn. Kokai Tokkyo Koho JP 06 09564, 1994; *Chem. Abstr.* **1994**, *121*, 83082; (b) Privitera, P. J.; Blickenstaff, T.; Gaffney, T. E.; Mohammed, S. *J. Pharmacol. Exp. Ther.* **1971**, *176*, 655–661.
9. Kono, Y.; Kojima, E.; Saito, K.; Kudo, S.; Sekoe, Y. Jpn. Kokai Tokkyo Koho JP 06 56788, 1994; *Chem. Abstr.* **1994**, *121*, 157536.
10. Carling, R. W.; Leeson, P. D.; Moore, K. W.; Smith, J. D.; Moyes, C. R.; Mawer, I. M.; Thomas, S.; Chan, T.; Baker, R.; Foster, A. C.; Grimwood, S.; Kemp, J. A.; Marshall, G. R.; Tricklebank, M. D.; Saywell, K. L. *J. Med. Chem.* **1993**, *36*, 3397–3408.
11. Kennewell, P. D.; Clements-Jewery, S.; Westwood, R. Brit. U.K. Patent Appl. GB 2192000, 1987; *Chem. Abstr.* **1988**, *109*, 54675.
12. Gerster, J. F.; Rohlfing, S. R.; Pecore, S.; Winandy, R. M.; Stern, R. M.; Landmesser, J. E.; Olsen, R. A.; Gleason, W. B. *J. Med. Chem.* **1987**, *30*, 839–843.
13. Vecchietti, V.; Clarke, G. D.; Colle, R.; Giardina, G.; Petrone, G.; Sbacchi, M. *J. Med. Chem.* **1991**, *34*, 2624–2633.
14. Singer, J. M.; Barr, B. M.; Coughenour, L. L.; Gregory, T. F.; Walters, M. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4560–4563.
15. (a) Zanobini, A.; Brandi, A.; de Meijere, A. *Eur. J. Org. Chem.* **2006**, 1251–1255; (b) Enderlin, G.; Taillefumier, C.; Didierjean, C.; Chapleur, I. *Tetrahedron: Asymmetry* **2005**, *16*, 2459–2474; (c) Raunak, R.; Kumar, V.; Mukherjee, S.; Poonam, P.; Prasad, A. K.; Olsen, K. E.; Schaeffer, S. J. C.; Sharma, S. K.; Watterson, A. C.; Errington, W.; Parmar, V. S. *Tetrahedron* **2005**, *61*, 5687–5697; (d) Dugovic, B.; Fisera, L.; Hametner, C.; Pronayova, N. *ARKIVOC* **2003**, 162–169; (e) Cheng, Q.; Zhang, W.; Tagami, Y.; Oritani, T. *J. Chem. Soc., Perkin Trans.* **2001**, 452–456; (f) Ondrus, V.; Orsag, M.; Fisera, L.; Pronayova, N. *Tetrahedron* **1999**, *55*, 10425–10436; (g) Loupy, A.; Petit, A.; Bonnet-Delpon, D. *J. Fluorine Chem.* **1995**, *75*, 215–216; (h) Diaz-Ortiz, A.; Diez-Barra, E.; de la Hoz, A.; Prieto, P.; Moreno, A.; Langa, F.; Prange, T.; Neuman, A. *J. Org. Chem.* **1995**, *60*, 4160–4166.
16. Pfister, J.; Wymann, W. *Synthesis* **1983**, 38–40.