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Synthesis and Highly Diastereoselective Alkylation of Chiral N-[(*S,S*)-3,5-Bis(1-methoxyethyl)-1,2,4-triazol-4-yl]arylimines

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Abstract: *(S,S)-4-Amino-3,5-bis(1-hydroxyethyl)-1,2,4-triazole 2 (SAT) (from (S)-lactic acid and hydrazine hydrate) reacted with substituted benzaldehydes 6 to afford N-[(S,S)-3,5-bis(1-hydroxyethyl)-1,2,4-triazol-4-yl]arylimines 3 in excellent yield. Protection of the hydroxyl groups in compounds 3 was accomplished using methyl tosylate under mild conditions to give N-[(S,S)-3,5-bis(1-methoxyethyl)-1,2,4-triazol-4-yl]arylimines 4 in very high yield. Subsequent reactions of 4 with Grignard reagents afforded compounds 5 with good to excellent diastereoselectivities in good yield.* Copyright © 1996 Elsevier Science Ltd

The 1,2-addition of carbon nucleophiles to imines and hydrazones is of great synthetic value for the synthesis of amines, and the potential for using this reaction for asymmetric synthesis has been realized. Numerous methods exist in the literature for their transformation into chiral amines with high optical purity and consist of the addition of organometallic reagents to chiral imines[1] or hydrazones,[2] or to achiral imines catalyzed by chiral ligands.[3] The most widely used reagents for this transformation are the SAMP/RAMP reagents developed by Enders,[2e,g,h,j,k] excellent but expensive chiral auxiliaries requiring numerous synthetic steps from slightly cheaper chiral materials.

Our recent synthetic successes with benzotriazole methodology[4] directed our attention towards using the known[5] C_2-symmetric chiral (*S,S*)-4-amino-3,5-bis(1-hydroxyethyl)-1,2,4-triazole **2** as a chiral auxiliary, since few examples existed in the literature where C_2-symmetric chiral auxiliaries had been used for asymmetric induction in a CN double bond.[6] Advantages associated with compound **2** include: i) **2** is easily synthesized

from cheap and commercially available (*S*)-lactic acid and hydrazine hydrate; ii) C_2-symmetric chiral auxiliaries such as **2** are expected to give higher diastereoselectivities than those chiral auxiliaries containing no symmetry.[7]

We herein report the use of this novel C_2-symmetric triazole as a chiral auxiliary for the nucleophilic 1,2-addition reaction of Grignard reagents to the CN double bond of hydrazones **4** (Scheme 1).

RESULTS AND DISCUSSION

The enantiomerically pure (*S,S*)-4-amino-3,5-bis(1-hydroxyethyl)-1,2,4-triazole (SAT) **2** was prepared according to the procedure of Torres *et al*,[5] from (*S*)-lactic acid **1** in good yield (75-80%). Comparison of the $[\alpha]_D$ of compound **2** with that reported in the literature demonstrated that the condensation reaction had taken place without racemization. Chiral triazole **2** was then reacted with the corresponding benzaldehydes **6** in the presence of a catalytic amount of *p*-toluenesulfonic acid in refluxing toluene, to afford the highly crystalline Schiff bases **3** as single geometrical isomers in excellent yields (90-98%).

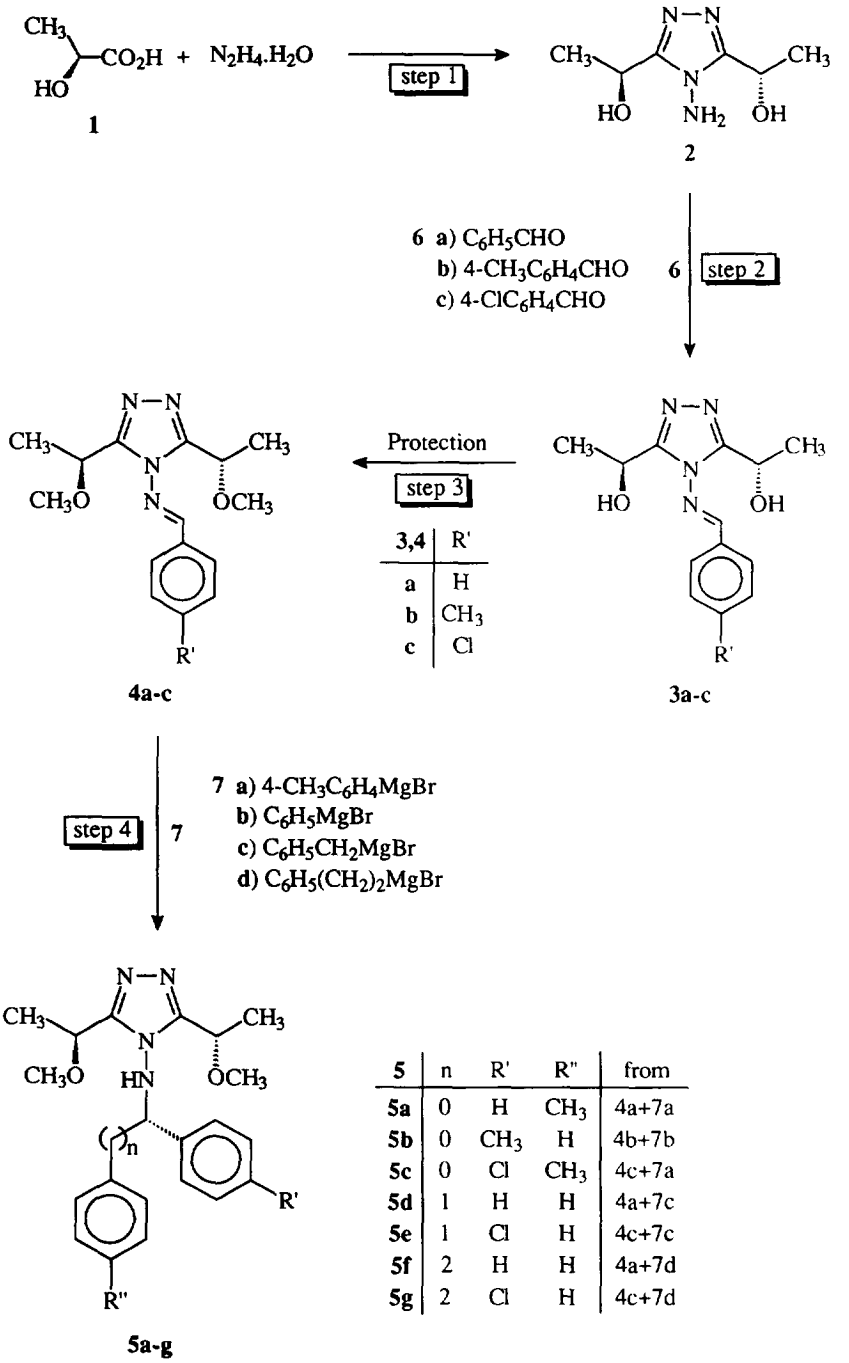
The geometrical conformation of the CN double bond was determined by carrying out NOEDIF[8] experiments on compound **3a**. Irradiation of the azomethine proton at 9.03 ppm yielded a positive NOE at 7.95 ppm (*ortho* position on the phenyl ring), at 4.95 ppm (position 1 on the ethyl chain) and 5.63 ppm (hydroxylic proton), and a negative NOE at 7.62 ppm (*meta* position on the phenyl ring). Conversely, irradiation of the protons on position 1 of the ethyl chain produced positive NOE's at the azomethine proton (9.03 ppm) and at the hydroxylic proton (5.63 ppm). Thus the geometrical conformation of the CN double bond in compound **3a** is *E* as expected and evidenced in the literature.[9]

Protection of the free hydroxyl groups was successfully accomplished by reacting the hydrazones **3** with sodium hydride and methyl tosylate using DMF as solvent, to generate the corresponding protected chiral hydrazones **4** in excellent yields 88-98% (Scheme 1).

Treatment of the protected hydrazones **4a-c** with various aryl and aryl alkyl Grignard reagents (3-4 equivalents) at -78°C, using toluene as the solvent, afforded the resulting amines **5** in 60-76% yields with diastereoselectivities ranging from 70% to ≥99% (Table 1). The diastereoisomeric excesses were measured by ^{1}H NMR spectroscopy and by gas chromatographic analysis.

Table 1. Diastereoselectivities of Compounds **5a-g**.

Product	Diastereoselectivities (%)	
	by ^{1}H NMR	by GC
5a	94	93
5b	70	70
5c	85	96
5d	≥95	96
5e	≥95	98
5f	91	83
5g	≥95	≥99



1

2

4a-c

3a-c

5a-g

5	n	R'	R"	from
5a	0	H	CH_3	4a+7a
5b	0	CH_3	H	4b+7b
5c	0	Cl	CH_3	4c+7a
5d	1	H	H	4a+7c
5e	1	Cl	H	4c+7c
5f	2	H	H	4a+7d
5g	2	Cl	H	4c+7d

Scheme 1

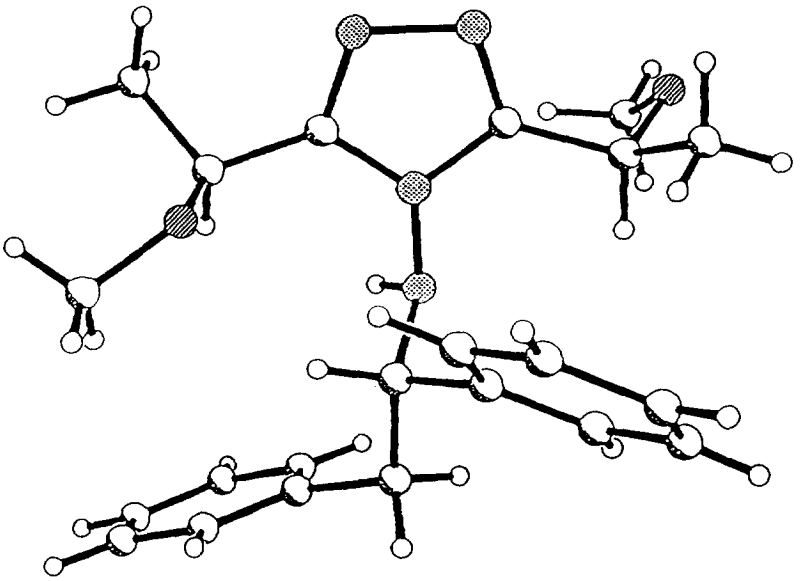


Figure 1. X-ray structure of compound **5d**.

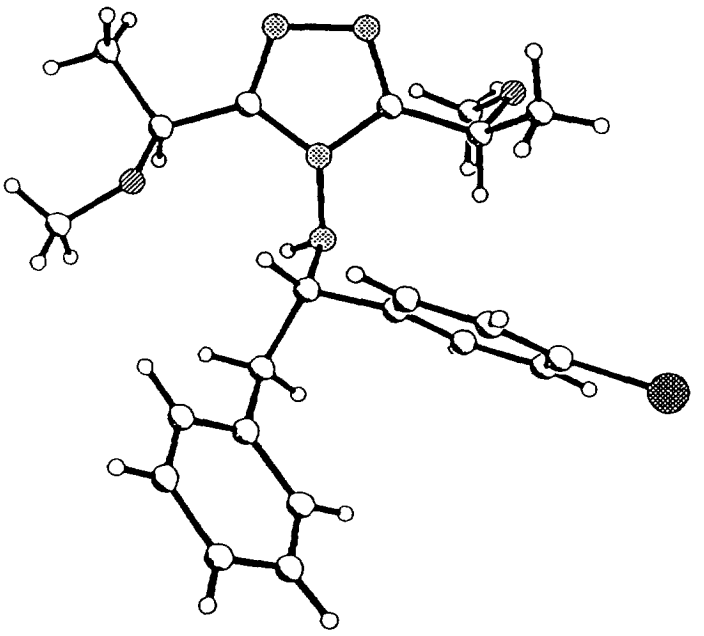


Figure 2. X-ray structure of compound **5e**.

The X-ray crystal structures of **5d** and **5e** were determined. Figures 1 and 2 show perspective views of the two structures, which both confirm the molecular structures and determines the configuration of the newly formed stereocenter to be *S*, in both cases. The triazole rings are each planar to within 0.001 Å. Interestingly in both structures the methoxyethyl substituents have similar unsymmetrical conformations with one methyl carbon (C22) and one hydrogen (H51) lying approximately coplanar with the triazole ring. The major difference between the two structures is in the conformations of the benzyl groups; in **5d** the two phenyl groups are *anti*, while in **5e** they are *gauche*. The bond lengths and angles lie within the normal ranges for related compounds. In both structures the NH group is involved in a weak linear hydrogen bond to a triazole N3 nitrogen of an adjacent molecule related by a screw axis, with N...N separations of 3.13(1) and 2.98(1) Å for **5d** and **5e**, respectively.

This is in agreement with our proposed mode of addition *via* chelation of one mole of Grignard reagent to both the methoxy group and the imine nitrogen, thus forming a fixed 6-membered transition state, which intramolecularly delivers the carbon nucleophile to the *si*-face of the imine (Figure 3). Thus we feel that we can predict the configuration of the other compounds in the series, all of them possessing the *S*-configuration except for compound **5b** which is believed to be in the *R*-configuration from our proposed transition state simply due to the higher (Prelog-Cahn-Ingold) priority of the added aryl group over the initially present aryl group. To realize the full potential of the chiral triazole as a chiral auxiliary our efforts are now directed towards the removal of this chiral auxiliary.

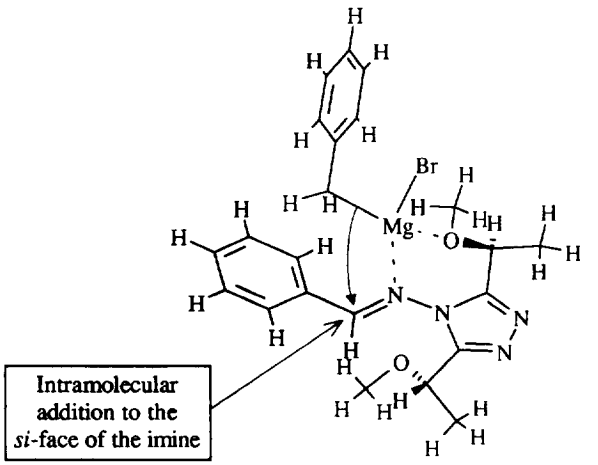


Figure 3

EXPERIMENTAL

General

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Gemini 300 MHz spectrometer; J values are given in Hz. Elemental

analyses were performed on a Carlo Erba-1106 instrument. $[\alpha]_D$ were recorded on a Perkin Elmer 341 polarimeter at 20°C. Gas Chromatographic analyses were run on a Hewlett Packard 5890 Gas Chromatograph. Toluene was predried and freshly distilled from sodium and benzophenone. DMF was dried over molecular sieves. Column chromatography was carried out on MCB silica gel (230-400 mesh).

X-Ray Crystallography

All measurements were made with a Siemens P4s four-circle diffractometer, operating at -115°C, using Mo*K*α (λ = 0.71073 Å) radiation. Cell constants were determined by least-squares refinements of at least 25 accurately centered reflections. Intensities were corrected for Lorentz-polarization effects but not for absorption. The structures were solved by direct methods using SHELXS[10] and refined on F^2, using all data, with SHELXL-93.[11] All non-hydrogen atoms were refined anisotropically. The C-H hydrogens were included in calculated positions with isotropic displacement parameters equal to 1.2 times the isotropic equivalent of their carrier carbons, and with the rotational orientations of the methyl group hydrogens deduced from circular Fourier syntheses. The positions of the N-H hydrogens were refined. The functions minimized were $\Sigma w(F_o^2 - F_c^2)$, with $w = [\sigma^2(F_o^2) + aP^2]^{-1}$ where $P = [\max(F_o^2) + 2F_c^2]/3$. Full tables of atom coordinates, bonding geometry, displacement parameters and structure factors are available from the author PJS.

Crystal Data for ***5d****:* $C_{22}H_{28}N_4O_2$, Mr = 380.48, colorless block, 0.73 x 0.53 x 0.53 mm, orthorhombic, space group $P2_12_12_1$, a = 9.446(2), b = 11.740(1), c = 18.620(3) Å, V = 2065(1) $Å^3$, Z = 4, D_{calc} = 1.224 g cm^{-3}, μ = 0.80 cm^{-1}, F(000) = 816, $2\theta_{max}$ = 60°, 3393 reflections, final wR = 0.1067 for all data (a = 0.0533), R = 0.0494 for 1887 data with $I>2\sigma(I)$.

Crystal Data for ***5e****:* $C_{22}H_{27}N_4O_2Cl$, Mr = 414.93, colorless block, 0.45 x 0.42 x 0.31 mm, monoclinic, space group $P2_1$, a = 10.150(1), b = 10.680(2), c = 10.593(2) Å, β = 95.27(2) °, V = 1143.4(3) $Å^3$, Z = 2, D_{calc} = 1.205 g cm^{-3}, μ = 1.91 cm^{-1}, F(000) = 440, $2\theta_{max}$ = 60°, 3492 reflections, final wR = 0.1038 for all data (a = 0.0474), R = 0.0497 for 1925 data with $I>2\sigma(I)$.

(S,S)-4-Amino-3,5-bis(1-hydroxyethyl)-1,2,4-triazole 2. (m.p. 130-132°C, $[\alpha]_D$=+23.9° at 20°C (c=0.015 g/mL, water); lit.[5a] m.p. 130-132°C, $[\alpha]_D$=+22.3° at 25°C (c=1.5, water)) was prepared according to the literature procedure described by Torres *et al*;[5] δ_H(d_6-DMSO): 1.48 (d, 6H, J =6.6 Hz), 4.86-4.95 (m, 2H), 5.40 (d, 2H, J=5.8 Hz), 5.77 (s, 2H); δ_C(d_6-DMSO): 20.9, 59.3, 156.4. For $C_6H_{12}N_4O_2$: Anal. Calcd: C, 41.85; H, 7.02; N, 32.54. Found: C, 42.17; H, 7.10; N, 32.47.

General Procedure for the Condensation of Aromatic Aldehydes with (S,S)-4-Amino-3-5-bis(1-hydroxyethyl)-1,2,4-triazole

(*S,S*)-4-Amino-3,5-bis(1-hydroxyethyl)-1,2,4-triazole **2** (4.3 g, 25 mmol) , the corresponding aromatic aldehyde (25 mmol) and a catalytic amount of *p*-toluenesulfonic acid (30 mg) were heated in toluene (25 mL) under reflux for 7 h. The solvent was removed under reduced pressure to give a solid which was recrystallized from ethanol.

N-[(S,S)-3,5-Bis(1-hydroxyethyl)-1,2,4-triazol-4-yl]phenylimine 3a. white solid, yield=90%, m.p. 203-205° C, $[\alpha]_D$=+79.4° at 20°C (c=0.01 g/mL, methanol); δ_H(d_6-DMSO): 1.55 (d, 6H, J=6.6 Hz), 4.93-4.97 (m, 2H), 5.63 (d, 2H, J=6.0 Hz), 7.59-7.66 (m, 3H), 7.95 (d, 2H, J=6.8 Hz), 9.03 (s, 1H); δ_C(d_6-DMSO): 21.0, 59.8,

128.9, 129.1, 132.3, 132.7, 153.4, 166.4. For $C_{13}H_{16}N_4O_2$: Anal. Calcd: C, 59.99; H, 6.20; N, 21.52. Found: C, 59.93; H, 6.24; N, 21.72.

N-[(S,S)-3,5-Bis(1-hydroxyethyl)-1,2,4-triazol-4-yl]-4-methylphenylimine 3b. white solid, yield=98%, m.p. 174-175°C, $[\alpha]_D$=+70.0° at 20°C (c=0.01g/mL, methanol); δ_H(d_6-DMSO): 1.54 (d, 6H, J=6.6 Hz), 2.41 (s, 3H), 4.89-4.96 (m, 2H), 5.63 (br s, 2H), 7.40 (d, 2H, J=7.8 Hz), 7.83 (d, 2H, J=8.0 Hz), 8.96 (s, 1H); δ_C(d_6-DMSO): 21.0, 21.3, 59.8, 128.9, 129.6, 129.7, 143.1, 153.4, 166.6. For $C_{14}H_{18}N_4O_2$: Anal. Calcd: C, 61.30; H, 6.61; N, 20.42. Found: C, 61.20; H, 6.58; N, 20.13.

N-[(S,S)-3,5-Bis(1-hydroxyethyl)-1,2,4-triazol-4-yl]-4-chlorophenylimine 3c. white solid, yield=95%, m.p. 192-193°C, $[\alpha]_D$=+55.1° at 20°C (c=0.01g/mL, methanol); δ_H(d_6-DMSO): 1.54 (d, 6H, J=6.4 Hz), 4.94-4.96 (m, 2H), 5.61 (br s, 2H), 7.66 (d, 2H, J=8.5 Hz), 7.96 (d, 2H, J=8.3 Hz), 9.03 (s, 1H); δ_C(d_6-DMSO): 20.9, 59.8, 129.2, 130.5, 131.2, 137.3, 153.5, 164.8. For $C_{13}H_{15}ClN_4O_2$: Anal. Calcd: C, 52.98; H, 5.13; N, 19.01. Found: C, 53.11; H, 5.07; N, 18.73.

General Procedure for the Protection of the Hydroxyl Groups in Compounds 3

To a well stirred suspension of 95% sodium hydride (1.6 g, 60 mmol, 2.4 equiv.) in dry DMF (50 mL) under argon was added hydrazone **3** (25 mmol). The reaction mixture was stirred at r.t. for 10 min. before adding methyl tosylate (11.16g, 60 mmol, 2.4 equiv.) and stirring the reaction mixture at r.t. for 5 h. This was then quenched with water (50 mL) and extracted with ethyl acetate (3 x 30 mL) to give **4** (88-98%).

N-[(S,S)-3,5-Bis(1-methoxyethyl)-1,2,4-triazol-4-yl]phenylimine 4a. white solid, yield=97%, m.p. 57-58°C, $[\alpha]_D$=-116.3° at 20°C (c=0.01g/mL, methanol); δ_H($CDCl_3$): 1.65 (d, 6H, J=6.7 Hz), 3.36 (s, 6H), 4.76 (q, 2H, J=6.8 Hz), 7.54-7.62 (m, 3H), 7.89-7.92 (m, 2H), 8.83 (s, 1H); δ_C($CDCl_3$): 17.1, 55.8, 70.1, 128.8, 129.0, 131.7, 132.8, 151.7, 167.1. For $C_{15}H_{20}N_4O_2$: Anal. Calcd: C, 62.48; H, 6.99; N, 19.43. Found: C, 62.32; H, 7.43; N, 19.53.

N-[(S,S)-3,5-Bis(1-methoxyethyl)-1,2,4-triazol-4-yl]-4-methylphenylimine 4b. white solid, yield=88%, m.p. 57-58°C, $[\alpha]_D$=-117.8° at 20°C (c=0.01g/mL, methanol); δ_H($CDCl_3$): 1.64 (d, 6H, J=6.8 Hz), 2.47 (s, 3H), 3.36 (s, 6H), 4.75 (q, 2H, J=6.8 Hz), 7.30-7.36 (m, 2H), 7.79 (d, 2H, J=8.1 Hz), 8.75 (s, 1H); δ_C($CDCl_3$): 17.3, 21.7, 56.1, 70.4, 129.1, 129.2, 129.9, 144.0, 151.9, 167.5. For $C_{16}H_{22}N_4O_2$: Anal. Calcd: C, 63.54; H, 7.34; N, 18.54. Found: C, 63.50; H, 7.54; N, 18.38.

N-[(S,S)-3,5-Bis(1-methoxyethyl)-1,2,4-triazol-4-yl]-4-chlorophenylimine 4c. white solid, yield=98%, m.p. 73-74°C, $[\alpha]_D$=-105.6° at 20°C (c=0.01g/mL, methanol); δ_H($CDCl_3$): 1.64 (d, 6H, J=6.8 Hz), 3.36 (s, 6H), 4.77 (q, 2H, J=6.8 Hz), 7.52 (d, 2H, J=8.5 Hz), 7.84 (d, 2H, J=8.5 Hz), 8.83 (s, 1H); δ_C($CDCl_3$): 17.2, 55.9, 70.4, 129.5, 130.1, 130.4, 139.3, 151.9, 165.5. For $C_{15}H_{19}ClN_4O_2$: Anal. Calcd: C, 55.81; H, 5.93; N, 17.36. Found: C, 55.53; H, 6.17; N, 17.30.

General Procedure for the reaction of the Protected imines 4 with Grignard Reagents

The protected imine 4 (3 mL/mmol) was dissolved in toluene (30-50 mL/mmol) and cooled to -78°C. At this temperature 3-5 equiv. of Grignard reagent in THF (1 mL/mmol) were added dropwise to the solution at a rate of 20 mL/h. The reaction mixture was then stirred for 1 h at -78°C before being allowed to warm to room temperature overnight. This was then quenched with water (50 mL) and the resulting emulsion was extracted with ethyl acetate (3 x 30 mL). The organic extracts were then dried over anhydrous $MgSO_4$, filtered and evaporated to dryness to give the pure products.

4-(S-α-Phenyl-p-methylbenzylamino)-(S,S)-3,5-bis(1-methoxyethyl)-1,2,4-triazole 5a. white solid, yield=67%, m.p. 183-185°C, $[\alpha]_D$=-141.5° at 20°C (c=0.01g/mL, ethanol); $\delta_H(CDCl_3)$: 1.50 (d, 6H, J=6.6 Hz), 2.32 (s, 3H), 3.13 (s, 6H), 4.24 (q, 2H, J=6.6 Hz), 5.44 (d, 1H, J=5.2 Hz), 5.96 (d, 1H, J=5.5 Hz), 7.07-7.14 (m, 4H), 7.30-7.36 (m, 5H); $\delta_C(CDCl_3)$: 16.9, 21.1, 55.2, 68.9, 69.7, 127.6, 127.9, 128.1, 128.7, 129.6, 137.3, 138.3, 139.8, 154.4. $\delta_H(d_6$-benzene): 1.50 (d, 6H, J=6.6 Hz), 1.99 (s, 3H), 2.95 (s, 6H), 4.17 (q, 2H, J=6.5 Hz), 5.62 (d, 1H, J=5.8 Hz), 6.03 (d, 1H, J=5.8 Hz), 6.79 (d, 2H, J=8.0 Hz), 6.97 (d, 2H, J=8.0 Hz), 7.06-7.15 (m, 3H), 7.37 (d, 2H, J=7.2 Hz). For $C_{22}H_{28}N_4O_2$: Anal. Calcd: C, 69.45; H, 7.42; N, 14.72. Found: C, 69.60; H, 7.51; N, 14.73.

4-(R-α-Phenyl-p-methylbenzylamino)-(S,S)-3,5-bis(1-methoxyethyl)-1,2,4-triazole 5b. white solid, yield=76%, m.p. 134-135°C, $[\alpha]_D$=-157.3° at 20°C (c=0.01g/mL, ethanol); $\delta_H(CDCl_3)$: 1.51 (d, 6H, J=6.6 Hz), 2.34 (s, 3H), 3.16 (s, 6H), 4.24 (q, 2H, J=6.6 Hz), 5.46 (d, 1H, J=5.2 Hz), 5.99 (d, 1H, J=5.3 Hz), 7.16-7.34 (m, 9H); $\delta_C(CDCl_3)$: 16.9, 21.0, 55.1, 68.9, 69.7, 127.5, 128.1, 128.3, 128.9, 129.4, 136.6, 137.8, 140.4, 154.4. $\delta_H(d_6$-benzene): 1.49 (d, 6H, J=6.6 Hz), 2.09 (s, 3H) [1.99 (s, 3H)] (ratio 7.2:1), 2.96 (s, 6H), 4.17 (overlapped quartet, 1H, J=6.6 Hz) [4.20 (overlapped quartet, 2H, J=6.6 Hz)], 5.62 (d, 1H, J=5.5 Hz), 6.12 (d, 2H, J=5.5 Hz), [6.79 (d, 2H, J=7.9 Hz)], 6.90-7.15 (m, 6H), 7.29 (d, 2H, J=8.0 Hz) [7.38 (d, 2H, J=6.9 Hz)] (ratio 5.7:1). For $C_{22}H_{28}N_4O_2$: Anal. Calcd: C, 69.45; H, 7.42; N, 14.72. Found: C, 69.69; H, 7.52; N, 14.77.

4-(S-α-Chlorophenyl-p-methylbenzylamino)-(S,S)-3,5-bis(1-methoxyethyl)-1,2,4-triazole 5c. white solid, yield=70%, m.p. 161-162°C, $[\alpha]_D$=-168.4° at 20°C (c=0.01g/mL, ethanol); $\delta_H(CDCl_3)$: 1.49 (d, 6H, J=6.6 Hz), 2.33 (s, 3H), 3.14 (s, 6H), 4.19 (q, 2H, J=6.6 Hz), 5.43 (d, 1H, J=5.8 Hz), 6.03 (d, 1H, J=5.8 Hz), 7.04 (d, 2H, J=8.2 Hz), 7.13 (d, 2H. J=7.9 Hz), 7.32 (s, 4H); $\delta_C(CDCl_3)$: 16.6, 21.0, 54.9, 68.3, 69.4, 128.1, 128.7, 128.8, 129.7, 133.7, 136.9, 138.5, 138.5, 154.2. $\delta_H(d_6$-benzene): 1.46 (d, 6H, J=6.6 Hz), 2.01 (s, 3H) [2.09 (s, 3H)] (ratio 12.9:1), 2.95 (s, 6H) [2.93 (s, 6H)] (ratio 10.8:1), 4.19 (q, 2H, J=6.5 Hz), 5.54 (d, 1H, J=5.5 Hz), 6.20 (d, 1H, J=5.5 Hz), 6.81 (d, 2H, J=7.9 Hz), 6.89 (d, 2H, J=8.0 Hz), 7.11-7.18 (m, 4H). For $C_{22}H_{27}ClN_4O_2$: Anal. Calcd: C, 63.68; H, 6.56; N, 13.50. Found: C, 63.49; H, 6.55; N, 13.60.

4-(1S,2-Diphenylethylamino)-(S,S)-3,5-bis(1-methoxyethyl)-1,2,4-triazole 5d. white solid, yield=71%, m.p. 151-153°C, $[\alpha]_D$=-64.7° at 20°C (c=0.01g/mL ethanol); $\delta_H(CDCl_3)$: 1.38 (d, 6H, J=6.6 Hz), 3.21 (s, 6H), 3.15-3.22 (m, 2H), 4.12-4.19 (m, 2H), 4.44-4.51 (m, 1H), 5.54 (d, 1H, J=5.3 Hz), 7.14-7.31 (m, 10H); $\delta_C(CDCl_3)$: 16.7, 40.3, 54.6, 67.4, 68.8, 126.8, 128.0, 128.6, 128.7, 128.8, 129.4, 137.6, 139.4, 154.2. $\delta_H(d_6$-benzene): 1.43 (d, 6H, J=6.6 Hz), 2.98 (dd, 1H, J=8.0, 13.5 Hz), 3.05 (s, 6H), 3.31 (dd, 1H, J=6.6, 13.5 Hz),

4.33-4.35 (m, 2H), 4.61-4.70 (m, 1H), 6.14 (d, 1H, J=4.7 Hz), 6.93-6.99 (m, 4H), 7.00-7.07 (m, 4H), 7.15 (br s, 2H). For $C_{22}H_{28}N_4O_2$: Anal. Calcd: C, 69.45; H, 7.42; N, 14.72. Found: C, 69.55; H, 7.48; N, 14.68.

4-(S-α-p-Chlorophenyl-2-phenylethylamino)-(S,S)-3,5-bis(1-methoxyethyl)-1,2,4-triazole 5e. white solid, yield=69%, m.p. 146-147°C, $[\alpha]_D$=-49.9° at 20°C (c=0.01g/mL, ethanol); $\delta_H(CDCl_3)$: 1.46 (d, 6H, J=6.6 Hz), 3.07-3.24 (m, 2H), 3.24 (s, 6H), 4.26-4.33 (m, 2H), 4.49-4.57 (m, 1H), 5.58 (d, 1H, J=4.6 Hz), 7.11-7.15 (m, 4H), 7.24-7.31 (m, 5H); $\delta_C(CDCl_3)$: 16.7, 40.3, 54.7, 66.6, 68.8, 126.9, 128.6, 128.9, 129.3, 129.4, 134.5, 137.0, 137.8, 154.2. $\delta_H(d_6$-benzene): 1.42 (d, 6H, J=6.6 Hz), 2.87 (dd, 1H, J=8.8, 13.5 Hz), 3.04 (s, 6H), 3.27 (dd, 1H, J=6.0, 13.5 Hz), 4.41-4.43 (m, 2H), 4.56-4.62 (m, 1H), 6.30 (d, 1H, J=4.2 Hz), 6.84 (d, 2H, J=8.6 Hz), 6.91-7.06 (m, 7H). For $C_{22}H_{27}ClN_4O_2$: Anal. Calcd: C, 63.68; H, 6.56; N, 13.50. Found: C, 63.43; H, 6.51; N, 13.60.

4-(1S,3-Diphenylpropylamino)-(S,S)-3,5-bis(1-methoxyethyl)-1,2,4-triazole 5f. white solid, yield=65%, m.p. 154-155°C, $[\alpha]_D$=-40.6° at 20°C (c=0.01g/mL, ethanol); $\delta_H(CDCl_3)$: 1.44 (d, 6H, J=6.6 Hz), 2.21-2.26 (m, 2H), 2.48-2.70 (m, 2H), 3.20 (s, 6H), 4.12-4.20 (m, 3H), 5.52 (d, 1H, J=6.3 Hz), 7.09 (d, 2H, J=6.9 Hz), 7.18-7.38 (m, 8H); $\delta_C(CDCl_3)$: 16.5, 32.2, 34.6, 54.7, 65.3, 69.2, 126.2, 128.1, 128.4, 128.5, 128.7, 129.0, 139.4, 141.0, 154.2. $\delta_H(d_6$-benzene): 1.46 (d, 6H, J=6.6 Hz), 2.01-2.11 (m, 1H), 2.19-2.26 (m, 1H), 2.46-2.51 (m, 2H), 2.97 (s, 6H) [3.03 (s, 6H)] (ratio 21.2:1), 4.20-4.32 (m, 3H), 5.81 (d, 1H, J=5.9 Hz), 6.96-7.15 (m, 10H). For $C_{23}H_{30}N_4O_2$: Anal. Calcd: C, 70.02; H, 7.66; N, 14.20. Found: C, 70.17; H, 7.94; N, 14.14.

4-(S-α-p-Chlorophenyl-3-phenylpropylamino)-(S,S)-3,5-bis(1-methoxyethyl)-1,2,4-triazole 5g. white solid, yield=60%, m.p. 150-151°C, $[\alpha]_D$=-46.6° at 20°C (c=0.01g/mL, ethanol); $\delta_H(CDCl_3)$: 1.46 (d, 6H, J=6.6 Hz), 2.18-2.23 (m, 2H), 2.41-2.52 (m, 1H), 2.59-2.68 (m, 1H), 3.21 (s, 6H), 4.12-4.28 (m, 3H), 5.56 (d, 1H, J=5.5 Hz), 7.06-7.38 (m, 9H); $\delta_C(CDCl_3)$: 16.6, 32.0, 34.5, 54.8, 64.4, 69.3, 126.2, 128.3, 128.5, 129.2, 129.5, 134.6, 137.8, 140.6, 154.2. $\delta_H(d_6$-benzene): 1.44 (d, 6H, J=6.5 Hz), 1.90-1.97 (m, 1H), 2.18-2.25 (m, 1H), 2.35-2.43 (m, 2H), 2.95 (s, 6H), 4.19-4.28 (m, 3H), 6.01 (d, 1H, J=5.0 Hz), 6.82 (d, 2H, J=8.5 Hz), 6.96 (d, 2H, J=6.9 Hz), 7.02 (d, 2H, J=8.5 Hz), 7.04-7.15 (m, 3H). For $C_{23}H_{29}ClN_4O_2$: Anal. Calcd: C, 64.40; H, 6.81; N, 13.06. Found: C, 64.64; H, 6.87; N, 13.08.

REFERENCES

1. a) Takahashi, H.; Suzuki, Y.; Inagaki, H.; *Chem. Pharm. Bull.* **1982** *30* 3160-3166. b) Suzuki, Y.; Takahashi, H.; *Chem. Pharm. Bull.* **1983** *31* 31-40. c) Takahashi, H.; Chida, Y.; Suzuki, T.; Yanaura, S.; Suzuki, Y.; Masuda, C.; *Chem. Pharm. Bull.* **1983** *31* 1659-1665. d) Takahashi, H.; Suzuki, Y.; Hori, T.; *Chem. Pharm. Bull.* **1983** *31* 2183-2191. e) Suzuki, Y.; Takahashi, H.; *Chem. Pharm. Bull.* **1983** *31* 2895-2898. f) Yamamoto, Y.; *Acc. Chem. Res.* **1987** *20* 243-249. g) Ukaji, Y.; Watai, T.; Sumi, T.; Fujisawa, T.; *Chem. Lett.* **1991** 1555-1558. h) Cainelli, G.; Giacomini, D., Mezzina, E.; Panunzio, M.; Zarantonello, P.; *Tetrahedron Lett.* **1991** *32* 2967-2970. i) Higashiyama, K.; Inoue, H.; Takahashi, H.; *Tetrahedron Lett.* **1992** *33* 235-238. j) Higashiyama, K.; Inoue, H.; Takahashi, H.; *Tetrahedron* **1994** *50* 1083-1092. k) Higashiyama, K.; Inoue, H.; Yamauchi, T.; Takahashi, H.; *J.*

Chem. Soc., Perkin Trans. 1 **1995** 111-115. l) Hashimoto, Y.; Takaoki, K.; Sudo, A.; Ogasawara, T.; Saigo, K.; *Chem. Lett.* **1995** 235-236.

2. a) Takahashi, H.; Tomita, K.; Otomasu, H.; *J. Chem. Soc., Chem. Commun.* **1979** 668-669. b) Takahashi, H.; Tomita, K.; Noguchi, H.; *Chem. Pharm. Bull.* **1981** *29* 3387-3391. c) Takahashi, H.; Inagaki, H.; *Chem. Pharm. Bull.* **1982** *30* 922-926. d) Takahashi, H.; Suzuki, Y.; *Chem. Pharm. Bull.* **1983** *31* 4295-4299. e) Enders, D.; Schubert, H.; Nübling, C.; *Angew. Chem. Int. Ed. Engl.* **1986** *25* 1109-1110. f) Claremon, D. A.; Lumma, P. K.; Phillips, B. T.; *J. Am. Chem. Soc.* **1986** *108* 8265-8266. g) Denmark, S. E.; Weber, T.; Piotrowski, D. W.; *J. Am. Chem. Soc.* **1987** *109* 2224-2225. h) Weber, T.; Edwards, J. P.; Denmark, S. E.; *Synlett* **1989** 20-22. i) Thiam, M.; Chastrette, F.; *Tetrahedron Lett.* **1990** *31* 1429-1432. j) Enders, D.; Funk, R.; Klatt, M.; Raabe, G.; Hovestreydt, E. R.; *Angew. Chem. Int. Ed. Engl.* **1993** *32* 418-421. k) Enders, D.; Schankat, J.; Klatt, M.; *Synlett* **1994** 795-797.
3. a) Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K.; *Tetrahedron Lett.* **1990** *31* 6681-6684. b) Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K.; *Tetrahedron Lett.* **1991** *32* 3095-3098. c) Katritzky, A. R.; Harris, P. A.; *Tetrahedron: Asymmetry* **1994** *3* 437-442. d) Berrisford, D. J.; *Angew. Chem. Int. Ed. Engl.* **1995** *34* 178-180.
4. a) Katritzky, A. R.; Yang, Z.; Cundy D. J.; *Aldrichimica Acta* **1994** *27* 31-38. b) Katritzky, A. R.; Lan, X.; *Chem. Soc. Rev.* **1994** 363-373. c) Katritzky, A. R.; Lan, X.; Fan, W.-Q.; *Synthesis* **1994** 445-456.
5. a) Alonso, J. M.; Martín, M. R.; de Mendoza, J.; Torres, T.; Elguero, J.; *Heterocycles* **1987** *26* 989-1000. b) Martínez-Díaz, M. V.; de Mendoza, J.; Santos, F.; Torres, T.; *Tetrahedron: Asymmetry* **1994** *5* 1291-1296.
6. a) Alexakis, A.; Lensen, N.; Mangeney, P.; *Tetrahedron Lett.* **1991** *32* 1171-1174. b) Alexakis, A.; Lensen, N.; Tranchier, J.-P.; Mangeney, P.; *J. Org. Chem.* **1992** *57* 4563-4565. c) Alexakis, A.; Lensen, N.; Tranchier, J.-P.; Mangeney, P.; Feneau-Dupont, J.; Declercq, J. P.; *Synthesis* **1995** 1038-1050.
7. Whitesell, J. K.; *Chem. Rev.* **1989** *89* 1581-1590.
8. Kinns, M.; Sanders, J. K. M.; *J. Magn. Reson.* **1984** *56* 518-520.
9. a) Kitaev, Yu. P.; Buzykin, B. I.; Troepol'skaya, T. V.; *Russ. Chem. Rev.* **1970** *39* 441-456. b) Corey, E. J.; Enders, D.; *Chem. Ber.* **1978** *111* 1337-1361.
10. Sheldrick, G. M.; *Acta Crystallogr.* **1990** *A46* 467.
11. Sheldrick, G. M.; *SHELXL-93*, University of Gottingen 1993.

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