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Chiral 1,2,4-Triazole Derivatives as Potential Synthetic Intermediates

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Abstract: *The potential of (S,S)-3,5-bis(α-trimethylsilyloxyethyl)-1,2,4-triazole 3 and (S,S)-3,5-bis(α-methoxyethyl)-1,2,4-triazole 9 as chiral synthetic intermediates has been investigated. Reaction of the chiral triazole 3 with ethyl 2-bromopropionate and subsequent treatment with LDA followed by quenching with an electrophile gave either esters 5 or lactones 6&7 in good yields with generally excellent diastereoselectivities.*

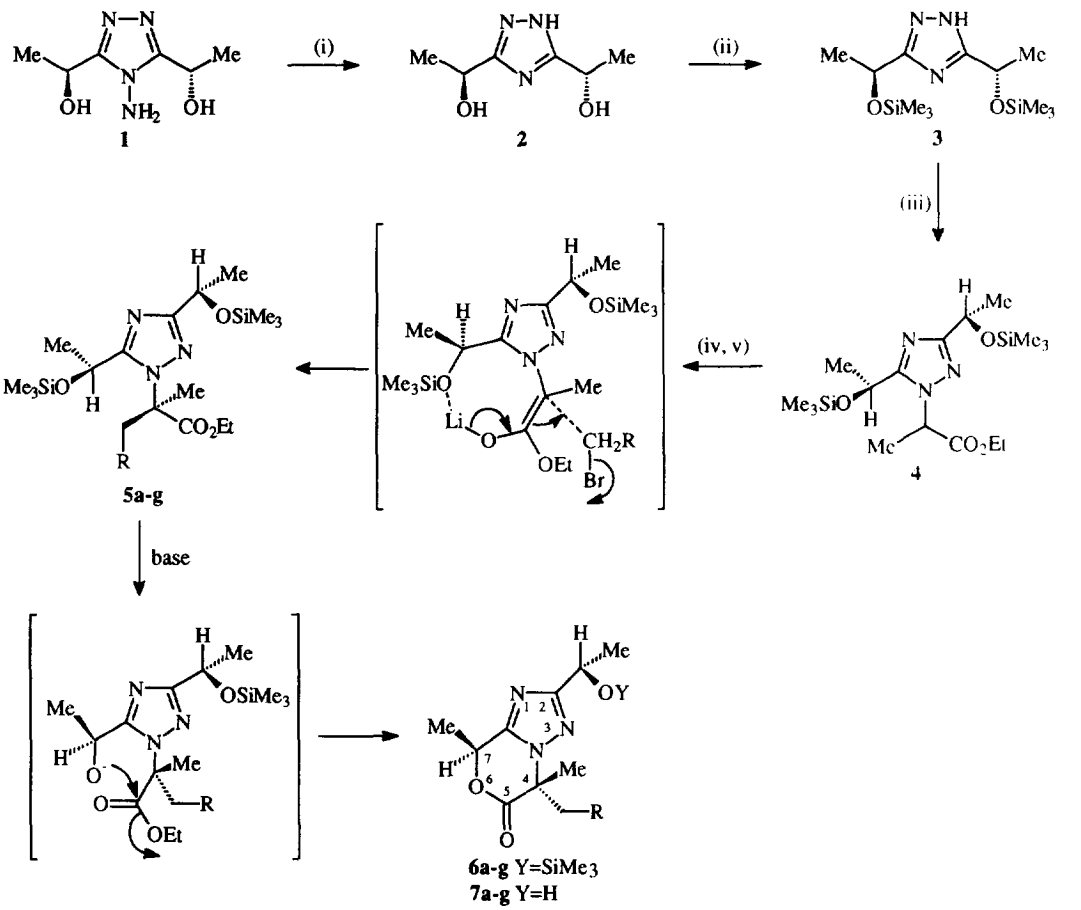
Optically pure α-substituted α-amino acids are of great importance as both enzyme inhibitors and pharmaceuticals.[1] Such non-proteinogenic amino acids have attracted much attention and have been synthesized by various methods,[2] including kinetic resolution,[3] alkylation of optically active amino acids,[4] Schmidt rearrangement,[5] and by the use of chiral templates[6] and chiral auxiliaries.[7] A few of these routes involved the use of heterocyclic intermediates as either chiral templates[6a] or chiral auxiliaries,[7a,d-f] both methods achieving high enantioselectivities.

We report herein the preparation and preliminary studies of the novel chiral triazoles (*S,S*)-3,5-bis(α-trimethylsilyloxyethyl)-1,2,4-triazole **3** and (*S,S*)-2,5-bis(α-methoxyethyl)-1,2,4-triazole **9** as a means of synthesizing optically pure α-substituted α-amino acids.

RESULTS AND DISCUSSION

Deaminated 1,2,4-triazole **2** was synthesized according to the procedure of Torres *et al.*[8] from the aforementioned amino 1,2,4-triazole **1**.[9] Comparison of the $[\alpha]_D$ of compound **2** with that reported in the literature demonstrated that deamination had taken place without racemization. The hydroxyl groups of **2** were then protected as trimethylsilyl ethers by reaction with 1,1,1,3,3,3-hexamethyldisilazane in refluxing THF. Product **3** was then refluxed with ethyl 2-bromopropionate in the presence of potassium carbonate in THF to

afford 1-ethoxycarbonylethyl-3,5-bis(1*S*-trimethylsilyloxyethyl)-1,2,4-triazole **4** as a 1:1 mixture of diastereoisomers in a 95% yield (Scheme 1). Diastereoisomeric mixture **4** was then treated with 1.5 equivalents of LDA at -15°C for 3 h, before quenching the resulting lithium enolate with ethyl bromide for 12 h while allowing the reaction to warm to room temperature. Column chromatography gave the compounds 1-(ethoxycarbonylethyl-1*R*-ethyl)-3,5-bis(1*S*-trimethylsilyloxyethyl)-1,2,4-triazole **5a** and 4*R*,7*S*-dimethyl-4-ethyl-2-(1*S*-trimethylsilyloxyethyl)-6H-1,2,4-triazolo-[5,1-c]oxazin-6-one **6a** in 13% and 60% yields, respectively. The structures of **5a** and the hydrolyzed product **7a** were confirmed by ^{1}H NMR, ^{13}C NMR, CHN analysis, GCMS, DQCOSY and NOE experiments.



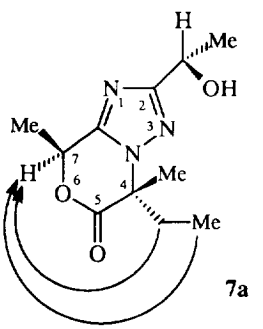
a: R = CH_3; **b**: R = n-C_3H_7; **c**: R = n-C_7H_{15}; **d**: R = Ph; **e**: R = *p*-$CH_3C_6H_4$; **f**: R = allyl; **g**: R = propargyl

(i) 6M HCl, $NaNO_2$, 0°C to r.t., 1h; (ii) $HN(SiMe_3)_2$, THF, reflux; (iii) $CH_3BrCHCO_2Et$, K_2CO_3, reflux; (iv) LDA, -15°C; (v) RCH_2X

Scheme 1

The ^{1}H NMR and ^{13}C NMR spectra of **7a** were assigned on the basis of DQCOSY and attached proton test (APT) techniques. The ^{1}H NMR spectrum of **7a** showed that a new quartet had appeared at 2.22 ppm with a coupling constant *J*=7.5 Hz and was assigned to the methylene group. Two characteristic quartets

located at 5.68 ppm (J=6.7 Hz) and 5.00 ppm (J=6.5 Hz), respectively, were assigned to the protons at the α-position of C-2 and C-7, respectively. With the help of the APT technique, the ^{13}C NMR spectrum of **7a** revealed that the characteristic signal of the α-C of position 2 resonated at 64.8 ppm, C-4 at 66.0 ppm, C-5 at 150.1 ppm and the α-C of position 7 at 71.9 ppm. Moreover, when the chemical shift reagent $Eu(fod)_3$ was added, the shapes of the signals in the ^1H NMR spectrum did not change except for some slight movement of the chemical shifts. The above results demonstrate that **7a** is a diastereoisomerically pure compound. Furthermore, NOE experiments were employed to establish the configuration of the newly formed stereocenter. Thus, irradiation of the α-H at 2.22 ppm (q) belonging to the ethyl group at the C-4 position enhanced the α-H of C-7 (2.1%), while positive enhancement of the α-H (0.47%) of C-7 was observed upon irradiation of the β-H at 0.71 ppm of the ethyl group (as shown in Figure 1). All these allowed us to establish unambiguously that the α-H of C-7 and the ethyl group at position 4 are on the same side of the triazole-ring, which means the absolute configuration of the induced chiral center (C-4) is *R*.



7a

Figure 1

In a similar way, the structure of **5a** was determined upon the basis of ^1H NMR, ^{13}C NMR, DQCOSY and APT techniques, all of which showed that **5a** was also diastereoisomerically pure. However, we could not use the NOE technique to determine its absolute configuration due to the α-H signals of C-3 and C-5 overlapping with each other in the ^1H NMR spectrum.

Treatment of the same lithium enolate of **4** with n-butyl bromide or n-octyl bromide, under the same reaction conditions but with stirring for 36 h gave compounds **7b** and **7c** exclusively in 78% and 73% yields, respectively. By comparison of these results with that of ethyl bromide, it was believed that compound **6a** came from the cyclization of **5a**. When compound **5a** was stirred with 0.2 equivalents of LDA at -15°C and allowed to warm to room temperature over 12 h it cyclized to give **6a** as a single diastereoisomer by ^1H NMR. This confirmed that **6a** was derived from **5a**, and that the configuration of **5a** is the same as that of **6a**. Moreover, if compound **6a** was stirred at room temperature for another 24 h in basic conditions, desilylation took place and afforded compound **7a** exclusively.

The above treatment of the lithium enolate of **4** was repeated using benzyl, 4-methylbenzyl, allyl and propargyl bromides as electrophiles to give the corresponding compounds **6/7(d-g)** in high yields. Once again, the NOE technique was employed to determine the stereochemistry of **6d**. A positive enhancement was observed at the α-H of C-7 while irradiating the methylene proton, which indicated that the configuration of C-4 is *R*. All the products except **7e** were oils, and a single crystal X-ray analysis of **7e** confirmed the absolute configuration deduced above by the NMR measurements. Figure 2 shows a perspective view of the X-ray crystal structure of the lactone **7e**, which both confirms the structure and determines the configuration of the newly formed stereocenter to be *R*. The triazole ring is planar to within 0.01 Å, while the lactone ring exists in a half-chair conformation. The 4-methylbenzyl group is oriented below the lactone ring so as to minimize both

intra- and inter-molecular repulsive interactions. The bond lengths and angles (submitted to Cambridge database) lie within the normal ranges for related compounds. The OH group is weakly hydrogen bonded to the triazole N4 nitrogen of an adjacent molecule related by a screw axis, with an N...O separation of 2.90(1) Å.

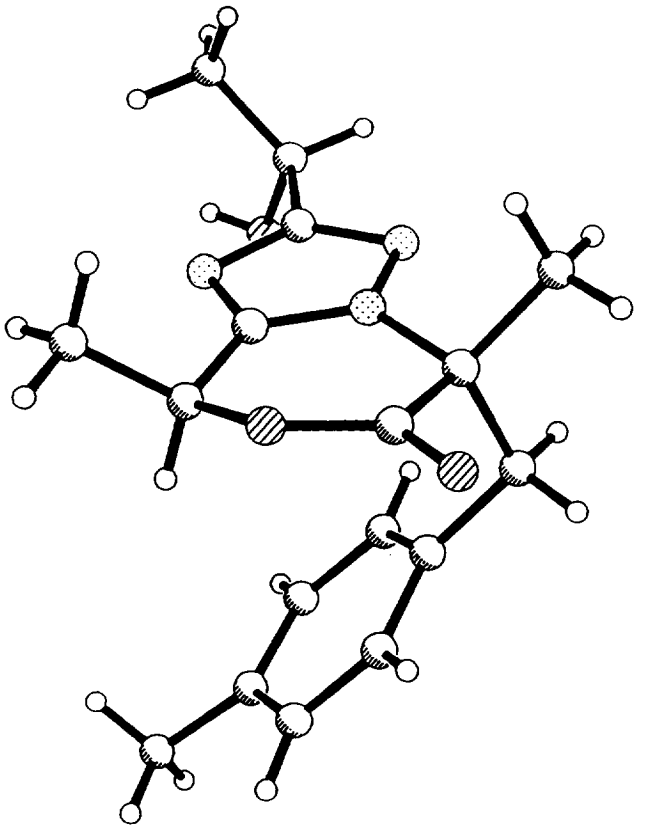


Figure 2. Perspective view of the X-ray crystal structure of compound 7e.

We proposed the reaction mechanism shown in Scheme 1: In the first step, 1-(α-ethoxycarbonylethyl)-3,5-bis(1*S*-trimethylsilyloxyethyl)-1,2,4-triazole **4** is deprotonated by LDA to result in the stereoselective formation of a lithium enolate geometrically defined by the chelation between lithium and the oxygen atom of the α-trimethylsilyloxyethyl group attached to postion 5 of the 1,2,4-triazole ring as illustrated in Scheme 1. This thus forms an 8-membered cyclic chelate as shown in Figure 3 with both the trimethylsilyl group and the methyl group blocking the *re*-face of the carbon/carbon double bond thus allowing approach of the alkyl halide from the less sterically hindered *si*-face of the enolate. This leads to the formation of the 1-(ethoxycarbonylethyl-1*R*-substituted)-3,5-bis(1*S*-trimethylsilyloxyethyl)-1,2,4-triazoles **5** in high diastereoselectivities and possessing the *R*-configuration at the newly formed stereocenter. Prolonged reaction times lead to the departure of the trimethylsilyl group and formation of the oxygen anion with the assistance of the catalytic excess of LDA. Cyclization then occurred, with this anion attacking the carbonyl group to form compounds **6** with displacement of the ethoxy group. When the reaction was left over a longer period of time (48 h), base hydrolysis of the remaining trimethylsilyl ether was completed to generate compound **7** as observed by NMR.

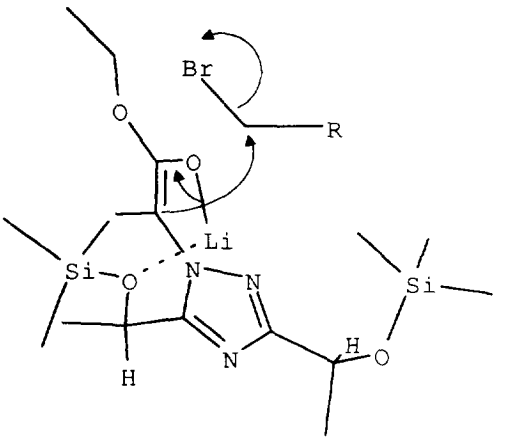
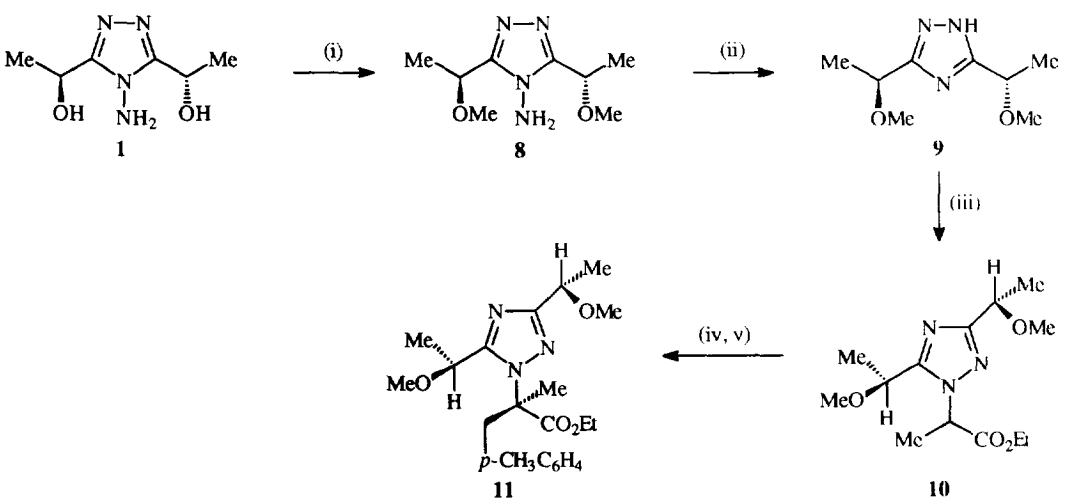


Figure 3

Changing the protecting group from a trimethylsilyl ether in compound **4** to a methyl ether and carrying out the lithiation reaction of **10** using 4-methylbenzyl bromide as the electrophile gave compound **11** as a mixture of diastereoisomers in a 96% yield. The diastereoisomeric excess was determined to be 60% by ^{1}H NMR spectroscopy (Scheme 2). Therefore we conclude that the bulky nature of the trimethylsilyl protecting group as compared with that of the methyl group increases the diastereoselectivity of the alkylation reaction from 60% to close to 100%.



(i) NaH, DMF, MeOTs, 0°C to r.t., 1h (79%); (ii) 6M HCl, $NaNO_2$, 0°C to r.t., 1h (84%); (iii) $CH_3BrCHCO_2Et$, K_2CO_3, reflux (98%); (iv) LDA, -15°C, 3h; (v) p-$CH_3C_6H_4CH_2Br$, -15°C to r.t. (93%, 60% d.e.).

Scheme 2

We have demonstrated that the chiral triazole (*S*,*S*)-3,5-bis(α-trimethylsilyloxyethyl)-1,2,4-triazole **3** is a good chiral inducer, giving high diastereoselectivities in virtually all cases. It is envisaged that the resulting

chiral lactones **6&7** will eventually be transformed into optically active α-substituted α-amino acids, or derivatives thereof, and work in this area is currently underway.

EXPERIMENTAL

General.

Melting points were determined on a hot-stage microscope. ^{1}H NMR, ^{13}C NMR and NOE experiments were carried on Varian VXR-300 or Varian VXR-500 instruments in deuteriochloroform ($CDCl_3$) or deuteriodimethylsulfoxide (DMSO-d_6) with tetramethylsilane (TMS) as the internal standard. Coupling constants (*J*) are quoted in Hz. GC/MS analyses were performed on a Hewlett Packard 5890 Series II gas chromatograph with a Hewlett Packard 5972 Series mass selective detector. Elemental analyses were performed in the chemistry department at the University of Florida. Tetrahydrofuran (THF) was dried by refluxing with sodium and benzophenone, and distilled immediately prior to use. Column chromatography was performed on MCB silica gel (230-400 mesh) with hexane and ethyl acetate as elutant Thin layer chromatography was carried out on precoated TLC plates (silica gel G60). LDA was purchased as a 1.5M solution in hexane.

X-ray Crystallography

All measurements were made with a Siemens P4s four-circle diffractometer, operating at room temperature, using Mo*K*α (λ = 0.71073 Å) radiation. A colorless crystal of dimensions 0.95 x 0.22 x 0.05mm was used. Cell constants were determined by least-squares refinement of 25 accurately centered reflections. Intensities were corrected for Lorentz-polarization effects but not for absorption. The structure was 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 hydrogens were included in calculated positions with isotropic displacement parameters equal to 1.2 times the isotropic equivalent of their carrier atoms. The function minimized was $\Sigma w(F_o^2 - F_c^2)$, with $w = [\sigma^2(F_o^2) + 0.0911P^2]^{-1}$ where $P = [\max(F_o^2) + 2F_c^2]/3$. Tables of atom coordinates, displacement parameters and structure factors are available as Supplementary Material and from the author PJS.

Crystal Data: $C_{17}H_{21}N_3O_3$, Mr = 315.4, monoclinic, space group $P2_1$, a = 9.268(2), b = 7.132(2), c = 12.724(3) Å, β = 90.17(2) °, V = 841.0(4) Å^3, Z = 2, D_{calc} = 1.245 g cm^{-3}, μ = 0.87 cm^{-1}, F(000) = 336, $2\theta_{max}$ = 50 °, 1627 reflections, final R = 0.066, wR = 0.151.

(*S,S*)-3,5-Bis(1-hydroxyethyl)-1,2,4-triazole (2): (m.p. 132-134°C, $[\alpha]_D$=-19.4° at 29°C (c=0.01 g/mL, methanol); lit.[8a] m.p. 134°C, $[\alpha]_D$=-18.5° at 25°C (c=0.01 g/mL, water)) was prepared according to the literature procedure described by Torres *et al*;[8a] ^{1}H NMR (d_6-DMSO): δ 4.76 (q, 2H, *J*=6.6 Hz), 1.40 (d, 6H, *J*=6.6 Hz); ^{13}C NMR ($CDCl_3$): δ 163.1, 62.4, 22.7.

(*S,S*)-3,5-Bis(α-trimethylsilyloxyethyl)-1,2,4-triazole (3): A mixture of (*S,S*)-3,5-bis(α-hydroxyethyl)-1,2,4-triazole (10 mmol, 1.57g) and 1,1,1,3,3,3-hexamethyldisilazane (30 mmol, 4.8g) was refluxed in THF (50 mL) for 8 h. Evaporation of the solvent gave a white solid which was recrystallized from ethyl acetate to give (*S,S*)-3,5-bis(α-trimethylsilyloxyethyl)-1,2,4-triazole **3** (2.85g, 95%) as a white solid. mp 133-134°C; ^{1}H NMR ($CDCl_3$): δ 5.05 (q, 2H, *J*=6.5 Hz), 1.54 (d, 6H, *J*=6.6 Hz), 0.13 (s, 18H); ^{13}C NMR ($CDCl_3$): δ 65.1, 23.8, -0.1 ppm. Anal. Calcd for $C_{12}H_{27}N_3O_2Si_2$ (301.54): C, 47.80; H, 9.03; N, 13.94. Found: C, 47.49; H, 9.16; N, 14.30.

1-(α-Ethoxycarbonylethyl)-3,5-bis(1*S*-trimethylsilyloxyethyl)-1,2,4-triazole (4): To a stirred solution containing equimolar amounts of compound **3** and ethyl 2-bromopropionate in THF were added two equivalents of potassium carbonate. The reaction mixture was stirred under reflux for 48 h before cooling and

extracting with ethyl acetate. The organic extracts were then washed with water and dried over $MgSO_4$. Removal of the solvent *via* rotary evaporation gave an oil which was subject to chromatography to give product **4** in 95% yield. ^1H NMR ($CDCl_3$): δ 5.71 (q, 1H, *J*=7.0 Hz), 5.61 (q, 1H, J=7.3 Hz), 5.29-5.18 (m, 2H), 4.96 (two overlapping quartets, 2H, *J*=6.5 Hz), 4.18 (two overlapping quartets, 4H, *J*=6.9 Hz), 1.77 (two overlapping triplets, 6H, *J*=7.0 Hz), 1.56-1.50 (m, 12H), 1.25-1.19 (m, 6H), 0.11 (two overlapping doublets, 18H, *J*=2.1 Hz), 0.07 (two overlapping doublets, 18H, *J*=2.5 Hz); ^{13}C NMR ($CDCl_3$): δ 169.4, 169.2, 164.9, 164.8, 157.3, 157.2, 65.3, 64.8, 64.6, 61.3, 61.3, 56.0, 55.8, 23.6, 23.4, 23.3, 23.2, 16.9, 16.4, 13.8, 13.7, -0.2, -0.3, -0.5, -0.6 ppm. Anal. Calcd for $C_{17}H_{35}N_3O_4Si_2$ (401.65): C, 50.84; H, 8.78; N, 10.46. Found: C, 50.47; H, 8.88; N, 10.44.

General procedure of compounds 5, 6 and 7: The preparation of 4-benzyl-4,7-dimethyl-2-(1*S*-trimethylsilyloxyethyl)-6H-1,2,4-triazolo-[5,1-c]oxazin-6-one **6d** will serve as an example. To a stirred solution of compound **4** (2 mmol, 0.8g) in THF (50 mL) at -15°C under nitrogen was added, dropwise, 1.5M LDA (1.1 equiv., 1.5 mL). The reaction mixture was stirred at -15°C for 5 h, before adding benzyl bromide (2 mmol, 0.35g) to this solution at -78°C and stirring overnight while allowing the reaction temperature to rise to ambient. The reaction mixture was then quenched with saturated aqueous NH_4Cl, extracted with ethyl acetate, washed with water and dried over $MgSO_4$. Removal of the solvent *via* rotary evaporation gave a sticky oil, which was subject to chromatography with hexane/ethyl acetate to give **6d** as a yellow oil (0.56g, 75%). ^1H NMR ($CDCl_3$): δ: 7.18-7.08 (m, 3H), 6.62 (d, 2H, *J*=7.8 Hz), 4.99 (q, 1H, *J*=6.2 Hz), 3.78 (q, 1H, *J*=6.5 Hz), 3.34 (d, 1H, *J*=13.7 Hz), 3.25 (d, 1H, *J*=13.7 Hz), 1.99 (s, 3H), 1.53 (d, 3H, *J*=5.9 Hz), 1.47 (d, 3H, *J*=6.8 Hz), 0.12 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 168.9, 168.2, 150.9, 134.0, 129.2, 128.8, 128.1, 71.2, 67.1, 65.0, 46.8, 25.5, 23.6, 19.4, 0.1 ppm. For $C_{19}H_{27}N_3O_3Si$ (373.53): GCMS: M^+=373; Anal. Calcd: C, 61.10; H, 7.29; N, 11.25. Found: C, 61.43; H, 7.56; N, 11.20.

4,7-Dimethyl-4-ethyl-2-(1*S*-trimethylsilyloxyethyl)-6H-1,2,4-triazolo-[5,1-c]oxazin-6-one 6a: colorless oil; yield=60%; ^1H NMR ($CDCl_3$): δ 5.68 (q, 1H, *J*=6.7 Hz), 5.00 (q, 1H, *J*=6.5 Hz), 2.22 (q, 2H, *J*=7.5 Hz), 1.86 (s, 3H), 1.83 (d, 3H, *J*=6.7 Hz), 1.56 (d, 3H, *J*=6.5 Hz), 0.72 (t, 3H, *J*=7.4 Hz), 0.12 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$): δ 168.8, 168.1, 150.1, 71.9, 66.0, 64.8, 33.6, 25.6, 23.2, 20.8, 8.4, -0.1 ppm; For $C_{14}H_{25}N_3O_3Si$ (311.46): GCMS: M^+=311; Anal. Calcd: C, 53.99; H, 8.09; N, 13.49. Found: C, 54.31; H, 8.27; N, 13.11.

1-(Ethoxycarbonylethyl-1*R*-ethyl)-3,5-bis(1*S*-trimethylsilyloxyethyl)-1,2,4-triazole 5a: colorless oil; yield=13%; ^1H NMR ($CDCl_3$): δ 5.01-4.92 (m, 2H), 4.20 (q, 2H, *J*=7.1 Hz), 2.44-2.20 (m, 2H), 1.80 (s, 3H), 1.59 (d, 3H, *J*=6.4 Hz), 1.55 (d, 3H, *J*=6.6 Hz), 1.25 (t, 3H, *J*=7.1 Hz), 0.88 (t, 3H, *J*=7.5 Hz), 0.12 (s, 9H), 0.07 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$): δ 172.0, 162.9, 157.5, 67.9, 65.0, 64.4, 61.6, 31.9, 24.0, 23.2, 23.1, 13.9, 8.4, 0.6, 0.0 ppm; For $C_{19}H_{39}N_3O_4Si_2$ (429.71): GCMS: M^+=429; Anal. Calcd: C, 53.11; H, 9.15; N, 9.78. Found: C, 53.44, H, 9.38; N, 9.68.

4*R*,7*S*-Dimethyl-4-ethyl-2-(1*S*-hydroxyethyl)-6H-1,2,4-triazolo-[5,1-c]oxazin-6-one 7a: ^1H NMR ($CDCl_3$): δ 5.67 (q, 1H, *J*=6.7 Hz), 4.99 (q, 1H, *J*=6.6 Hz), 2.70 (br. s, 1H), 2.22 (q, 2H, *J*=7.4 Hz), 1.86 (s, 3H), 1.82 (d, 3H, *J*=6.8 Hz), 1.60 (d, 3H, *J*=6.6 Hz), 0.71 (t, 3H, *J*=7.4 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ 168.8, 168.2, 150.3, 71.8, 66.2, 64.5, 33.7, 25.7, 22.4, 20.8, 8.6 ppm. HRMS (EI) Found $(M+1)^+$, 240.1300, $C_{11}H_{18}N_3O_3$ requires 240.1348. $[\alpha]_D$=-68.6° at 27°C (c=0.01 g/mL, chloroform). d.e. ≥95% by NMR, d.e. ≥ 99% by GCMS.

4*R*,7*S*-Dimethyl-2-(1*S*-hydroxyethyl)-4-propyl-6H-1,2,4-triazolo-[5,1-c]oxazin-6-one 7b: light yellow oil; yield=78%; ^1H NMR ($CDCl_3$): δ 5.62 (q, 1H, *J*=6.8 Hz), 4.94 (q, 1H, *J*=6.6 Hz), 2.14-2.08 (m, 2H,), 1.80 (s, 3H), 1.77 (d, 3H, *J*=6.8 Hz), 1.55 (d, 3H, *J*=6.6 Hz), 1.23-1.00 (m, 4H), 0.76 (t, 3H, *J*=7.3 Hz) ppm. ^{13}C

NMR ($CDCl_3$): δ 168.9, 168.2, 150.1, 71.7, 65.6, 64.3, 40.1, 26.2, 26.0, 22.4, 22.0, 20.7, 13.6 ppm. HRMS (EI) Found $(M+1)^+$, 268.1679, $C_{13}H_{22}N_3O_3$ requires 268.1661. $[\alpha]_D$=-55.1° at 29°C (c=0.01 g/mL, chloroform). d.e. ≥95% by NMR, d.e. ≥99% by GCMS.

4*R*,7*S*-Dimethyl-4-heptyl-2-(1*S*-hydroxyethyl)-6H-1,2,4-triazolo-[5,1-c]oxazin-6-one 7c: yellow oil; yield=73%; ^1H NMR ($CDCl_3$): δ 5.67 (q, 1H, *J*=6.7 Hz), 4.99 (q, 1H, *J*=6.6 Hz), 2.33-2.14 (m, 2H), 1.83 (d, 3H, *J*=6.8 Hz), 1.78 (s, 3H), 1.61 (d, 3H, *J*=6.6 Hz), 1.32-1.13 (m, 12H), 0.86 (t, 3H, *J*=6.9 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ 168.5, 168.3, 149.9, 72.0, 65.6, 64.5, 39.7, 31.7, 29.0, 29.0, 28.8, 26.4, 24.1, 22.5, 22.4, 21.2, 14.0 ppm. Anal. Calcd for $C_{17}H_{29}N_3O_3$ (323.44): C, 63.11; H, 9.04; N, 13.00. Found: C, 63.50; H, 9.33; N, 12.60. $[\alpha]_D$=-29.5° at 28°C (c=0.01 g/mL, chloroform). d.e. ≥95% by NMR, d.e. ≥99% by GCMS.

4*R*,7*S*-Dimethyl-2-(1*S*-hydroxyethyl)-4-(*p*-methylbenzyl))-6H-1,2,4-triazolo-[5,1-c]oxazin-6-one 7e: white solid m.p. 126-127°C; yield=95%; ^1H NMR ($CDCl_3$): δ 6.96 (d, 2H, *J*=7.9 Hz), 6.54 (d, 2H, *J*=8 Hz), 5.05-4.99 (m, 1H), 3.86 (q, 1H, *J*=6.9 Hz), 3.36 (d, 1H, *J*=13.5 Hz), 3.23 (d, 1H, *J*=13.5 Hz), 2.90 (br. s, 1H, OH), 2.26 (s, 3H), 2.03 (s, 3H), 1.63 (d, 3H, *J*=6.6 Hz), 1.53 (d, 3H, *J*=6.9 Hz). ^{13}C NMR ($CDCl_3$): δ 169.0, 168.2, 151.3, 138.1, 130.7, 129.6, 129.0, 71.0, 67.3, 64.7, 46.5, 25.3, 22.7, 21.0, 19.4 ppm. Anal. Calcd for $C_{17}H_{21}N_3O_3$ (315.37): C, 64.74; H, 6.71; N, 13.32. Found: C, 64.83; H, 6.74; N, 13.31. $[\alpha]_D$=-235.9° at 27 °C (c=0.01 g/mL, chloroform). d.e. ≥95% by NMR, d.e. ≥99% by GCMS.

4-Allyl-4*R*,7*S*-dimethyl-2-(1*S*-hydroxyethyl)-6H-1,2,4-triazolo-[5,1-c]oxazin-6-one 7f: yellow oil; yield=89%; ^1H NMR ($CDCl_3$): δ 5.63 (q, 1H, *J*=6.8 Hz), 5.49-5.35 (m, 1H), 5.09-4.97 (m, 3H), 3.90 (br. s, 1H), 2.88 (d, 2H, *J*=7.5 Hz), 1.90 (s, 3H), 1.80 (d, 3H, *J*=6.8 Hz), 1.61 (d, 3H, *J*=6.6 Hz), ppm. ^{13}C NMR ($CDCl_3$): δ 168.3, 168.1, 150.3, 129.7, 121.9, 71.7, 65.5, 64.1, 44.2, 25.4, 22.2, 20.3 ppm. Anal. Calcd for $C_{12}H_{17}N_3O_3$ (251.29): C, 57.34; H, 6.82. Found: C, 57.47; H, 6.98. $[\alpha]_D$=-111.2° at 29°C (c=0.01 g/mL, chloroform). d.e. ≥95% by NMR, d.e. ≥99% by GCMS.

4*R*,7*S*-Dimethyl-2-(1*S*-hydroxyethyl)-4-propargyl-6H-1,2,4-triazolo-[5,1-c]oxazin-6-one 7g: yellow oil; yield=85%; ^1H NMR ($CDCl_3$): δ 5.84 (q, 1H, *J*=6.8 Hz), 5.02-4.99 (m, 1H), 3.26 (br. s, 1H), 3.05-3.03 (m, 2H), 2.05-1.98 (m, 1H), 1.90 (s, 3H), 1.84 (d, 3H, *J*=6.8 Hz), 1.62 (d, 3H, *J*=6.6 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ 168.4, 167.9, 150.9, 72.9, 72.4, 64.8, 64.5, 30.9, 25.4, 22.3, 20.3 ppm. Anal. Calcd for $C_{12}H_{15}N_3O_3$ (249.27): C, 57.81; H, 6.07. Found: C, 58.10; H, 6.17. $[\alpha]_D$=-121.8° at 28°C (c=0.01 g/mL, chloroform). d.e. =62% by GCMS.

(*S*,*S*)-4-Amino-3,5-bis(1-methoxyethyl)-1,2,4-triazole 8: A dispersion of sodium hydride in mineral oil (60%, 10.0g, 0.25 mol) was washed with dry n-hexane (3x25 mL) before suspending in dry DMF (250 mL). This was then cooled in an ice-bath to 0°C before adding a solution of (*S*,*S*)-4-amino-3,5-bis(1-hydroxyethyl)1,2,4-triazole **1** (20.7g, 0.12 mol) in dry DMF (125 mL) dropwise over 10 minutes. This was then treated with methyl tosylate (46.5g, 0.25 mol) in dry DMF (100 mL) dropwise over 1 hour and the resulting mixture was then stirred at 0°C for a further 30 minutes and then at room temperature for an additional 1 hour. The reaction mixture was then evaporated to dryness and the resulting solid residue was extracted with a 1:1 mixture of chloroform:ethyl acetate (5x150 mL) and filtered, the solid residue being washed well and the filtrate being evaporated to dryness. The resulting residue was then columned on silica (500 g) using a 3:1 mixture of diethyl ether:methanol as eluant to give the pure product as a white solid (18.9 g, 79%). m.p. 66-70°C; ^1H NMR ($CDCl_3$): δ 5.28 (s, 2H), 4.78 (q, 2H, *J*=6.6 Hz), 3.34 (s, 6H), 1.65 (d, 6H, *J*=6.6 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ 153.7, 70.7, 56.2, 17.5 ppm. Anal. Calcd for $C_8H_{16}N_4O_2$ (200.24): C, 47.99; H, 8.05; N, 27.98. Found: C, 47.95; H, 8.27; N, 27.94. $[\alpha]_D$=-77.5° at 27°C (c=0.01 g/mL, chloroform).

(*S,S*)-3,5-Bis(1-methoxyethyl)-1,2,4-triazole 9: A solution of (*S,S*)-4-amino-3,5-bis(1-methoxyethyl)-1,2,4-triazole **8** (5g, 0.025 mol) in 6M HCl (37.5 mL) was cooled to -6°C using an ice/salt mixture before adding a solution of sodium nitrite (2.58g, 0.0375 mol) in water (25 mL) very slowly over *ca.* 70 minutes. Care was taken to ensure that the temperature did not rise above 5°C during the addition. The mixture was then stirred at 0°C for a further 15 minutes before allowing it to warm to room temperature and stirring for an additional 1 hour. The solution was then neutralized to pH=7 using saturated sodium bicarbonate solution and was then extracted well with chloroform. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and evaporated to dryness to give the pure product as a white solid (3.89g, 85%). m.p. 50-54°C; ^{1}H NMR ($CDCl_3$): δ 12.1 (br. s, 1H), 4.63 (q, 2H, *J*=6.5 Hz), 3.39 (s, 6H), 1.58 (d, 6H, *J*=6.6 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ 161.8, 72.9, 56.8, 20.0 ppm. Anal. Calcd for $C_8H_{15}N_3O_2$ (185.23): C, 51.88; H, 8.16; N, 22.69. Found: C, 51.57; H, 8.27; N, 22.63. $[\alpha]_D$=-110.6° at 26°C (c=0.01 g/mL, chloroform).

1-Ethoxycarbonylethyl-3,5-bis(1*S*-methoxyethyl)-1,2,4-triazole (10): To a stirred solution of (*S,S*)-3,5-bis(α-methoxymethyl)-1,2,4-triazole **9** (3.7g, 0.02 mol) and ethyl 2-bromopropionate (3.62g, 0.2 mol) in THF was added one equivalent of potassium carbonate monohydrate. The reaction mixture was stirred under reflux for 48 h before cooling to ambient temperature and extracting with ethyl acetate. The organic extracts were washed with water, dried over anhydrous magnesium sulfate, filtered and evaporated to dryness to give a light yellow oil; yield=98%; ^{1}H NMR ($CDCl_3$): δ 5.53-5.41 (m, 2H), 4.80-4.70 (m, 2H), 4.53-4.45 (m, 2H), 4.25-4.14 (m, 4H), 3.32-3.30 (m, 12H), 1.81 (d, 6H, *J*=7.2 Hz), 1.58-1.53 (m, 12H), 1.22 (t, 6H, *J*=7.1 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ 169.3, 169.3, 163.4, 163.2, 156.3, 156.0, 72.8, 72.7, 72.4, 61.6, 61.6, 56.8, 56.7, 56.6, 56.2, 56.1, 56.1, 19.9, 19.9, 19.6, 19.3, 16.8, 16.8, 13.9, 13.8 ppm. Anal. Calcd for $C_{13}H_{23}N_3O_4$ (285.34): C, 54.70; H, 8.13; N, 14.73. Found: C, 54.11; H, 8.35; N, 15.47.

1-[Ethoxycarbonylethyl-1-(*p*-methylbenzyl)]-3,5-bis(1*S*-methoxyethyl)-1,2,4-triazole (11): To a stirred solution of 1-ethoxycarbonylethyl-3,5-bis(1*S*-methoxyethyl)-1,2,4-triazole **10** (285mg, 1 mmol) in THF (10 mL) at -15°C was added LDA (1.1 equiv., 1.1 mmol). This was stirred at this temperature for 3 h before adding *p*-methylbenzyl bromide (1 mmol, 186mg) dissolved in THF (5 mL). The resulting mixture was allowed to stir for another 12 h while allowing it to warm to ambient temperature. This was then quenched with water and extracted with ethyl acetate before drying over anhydrous magnesium sulfate. Filtration followed by rotary evaporation to dryness gave a yellow oil; yield=96%; ^{1}H NMR ($CDCl_3$): δ 6.99 (d, 2H, *J*=6.8 Hz) [(6.96 (d, 2H, *J*=6.8 Hz)], 6.77 (d, 2H, *J*=6.8 Hz) [6.70 (d, 2H, *J*=7.8 Hz)], 4.53 (q, 1H, *J*=6.2 Hz), 4.45 (q, 1H, *J*=6.4 Hz), [4.41 (q, 1H, *J*=5.9 Hz)], [4.25 (q, 1H, *J*=6.8 Hz)], 4.19-4.10 (m, 4H), [3.66 (d, 1H, *J*=14.7 Hz)], 3.59 (d, 1H, *J*=13.7 Hz), 3.49 d, 1H, *J*=13.7 Hz), [3.35 (d, 1H, *J*=13.7 Hz)], [3.32 (s, 3H)], 3.26 (s, 3H), [3.22 (s, 3H)], 3.21 (s, 3H), 2.27 (s, 6H), 1.78 (s, 6H), 1.59 (d, 6H, *J*=5.9 Hz), 1.54 (d, 3H, *J*=6.8 Hz), [1.47 (d, 3H, *J*=6.8 Hz)], [1.26 (t, 3H, *J*=6.8 Hz)], 1.17 (t, 3H, *J*=6.8 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ 171.4, 161.1, 156.4, 136.5, 131.8, 130.1, 128.7, 72.9, 71.2, 70.7, 68.5, 61.6, 56.2, 54.9, 43.6, 43.1, 24.0, 23.4, 20.8, 20.0, 17.9, 17.3, 13.6 ppm. Anal. Calcd for $C_{21}H_{31}N_3O_4$ (389.23): C, 64.74; H 8.03; N, 10.79. Found: C, 64.41; H, 8.42; N, 10.70.

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