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Chiral 1,2,4-triazoles: stereoselective acylation and chlorination

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ABSTRACT

Acyl groups are transferred from diverse *N*- and *O*-acyl derivatives of chiral 3,5-bis-(1-hydroxyethyl)-[1,2,4]-triazole to amino acid esters enantioselectively, with 7% to 68% ee, depending on the temperature conditions and nature of the reagents. Thionyl chloride replaced the hydroxyl groups of (*S*)-1-[4-amino-5-((*S*)-1-hydroxy-ethyl)-[1,2,4]-triazol-3-yl]-ethanol **3** stereospecifically with inversion, as confirmed by X-ray analysis, which also revealed unusual crystal structures with asymmetric units comprising three molecules of 4-amino-3,5-bis(*R*-1-chloroethyl)-1,2,4-triazole **5** and four of 3,5-bis((*R*)-1-chloroethyl)-1*H*-1,2,4-triazole **6**.

1. Introduction

The acylation of alcohols, phenols, amines, and thiols by acyl chlorides, -anhydrides, and -benzotriazoles has been intensively explored and is well understood.[1,2] Acylative desymmetrization and resolution of alcohols give excellent results using cinchona-, metallocene-, and titanium-based catalysts.[3] However, the kinetic resolution of amines remains a significant challenge:[3] recent work has involved (i) chiral ketones;[4,5] (ii) chiral heterocycle-catalyzed kinetic enantioselective acylations;[6–10] and (iii) enzyme-mediated acylation[11–14] which is effective, but limited by substrate specificity.[15] The active site of an enzyme for selective catalysis is often a tiny fraction of the structure,[16] and indeed low-molecular weight peptides can catalyze enantioselective acyl transfer.[17,18]

The chiral resolution of racemic amines has recently been successfully carried out with two chiral acyl transfer agents: benzimidazolide **1a**[19,20] and quinazolinone **1b**[21] (Scheme 1).

Our group first used benzimidazole derivative **1c** successfully for asymmetric induction.[19] Another heterocycle (*S,S*)-4-amino-3,5-bis(1-hydroxyethyl)-1,2,4-triazole **3**, easily prepared[22] in enantiomerically pure form, can be selectively acylated at the hydroxyl groups and/or at the heterocycle nitrogen (Scheme 2). Compound **3** attracted our attention as a chiral-leaving group for the enantioselective acylation of alcohols, amines, and amino acids,[23,24] and we now report on the potential of O-, N-acylated 1,2,4-chiral triazoles as chiral acylating reagents for amines and amino acids.

2. Results and discussion

Chiral 1,2,4-triazoles,[22] readily prepared from L-lactic acid and hydrazine hydrate,[22,23,25] have been used in asymmetric synthesis.[24] In our hands, triazole **6**, obtained in two steps from **3**, was N-acylated with acyl chlorides to obtain **7**–**9**. Triazole **4** was acylated at the NH and OH groups to obtain **10**–**12**. Triacyltriazoles **11** and **12** each underwent hydrolysis at 20 °C in water or aqueous methanol to form diacyl triazoles **13** and **14**, respectively (Scheme 2).

Treatment of **3** with thionyl chloride at 50–70 °C for 2 h gave a mixture of (*R,R*)-**5** and (*R,S*)-**5** stereoisomers (ratio 12:1) in a total yield of 68%. Pure (*R,R*)-**5** isomer (50%) precipitated from the reaction mixture and was isolated easily by filtration. Extraction of the residual aqueous solution with dichloromethane gave a 1:1 mixture of **5** (*R,R*)/(*R,S*); the ratio was determined by NMR and HPLC. Reaction at 20 °C for 60 h increased the proportion of (*RS*)-**5**.

Deamination by nitrous acid of the (*R,R*)-**5** isomer at 0–5 °C proceeded without epimerization to give pure (*R,R*)-**6** as shown by X-ray, NMR, and chiral HPLC. Acylation of (*R,R*)-**6** by nitrobenzoyl chloride gave pure (*R,R*)-**8** $[\alpha]_D^{23} = -112.0$ (*c* 2, $CHCl_3$). However, benzoyl chloride and benzyl chloroformate under the same conditions converted (*R,R*)-**6** into mixtures of (*R,R*)-, (*R,S*)-, (*S,R*)-, and (*S,S*)-stereoisomers of **7** and **9**. The epimerization of the chiral centers of (*R,R*)-**6** during the reaction was assumed to be caused by Et_3N. Indeed (*R,R*)-**6** undergoes epimerization in the presence of Et_3N for 0.5 h in dichloromethane at 20 °C but is stable in an acid solution for 10 h, as demonstrated by specific rotation measurements. Complete epimerization of triazole (*R,R*)-**6** was observed in dichloromethane solution after 3 days at 25 °C. We believe that the higher reactivity of 4-nitrobenzoyl chloride, compared with benzoyl chloride and benzyl chloroformate, results in a faster capture of HCl by Et_3N and neutralization of reaction mixture, thus prevents epimerization to give enantiomerically pure (*R,R*)-**8**.

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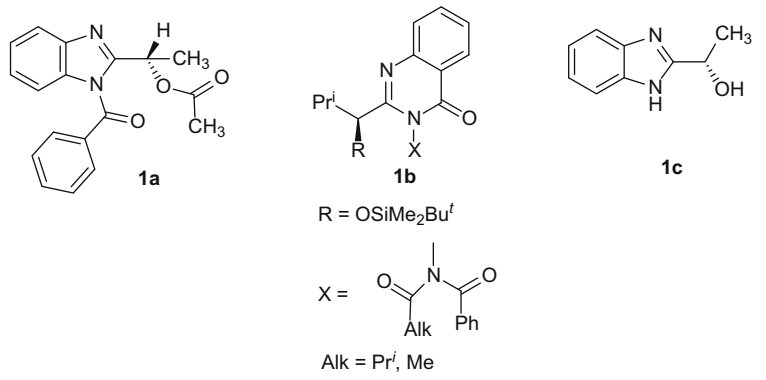
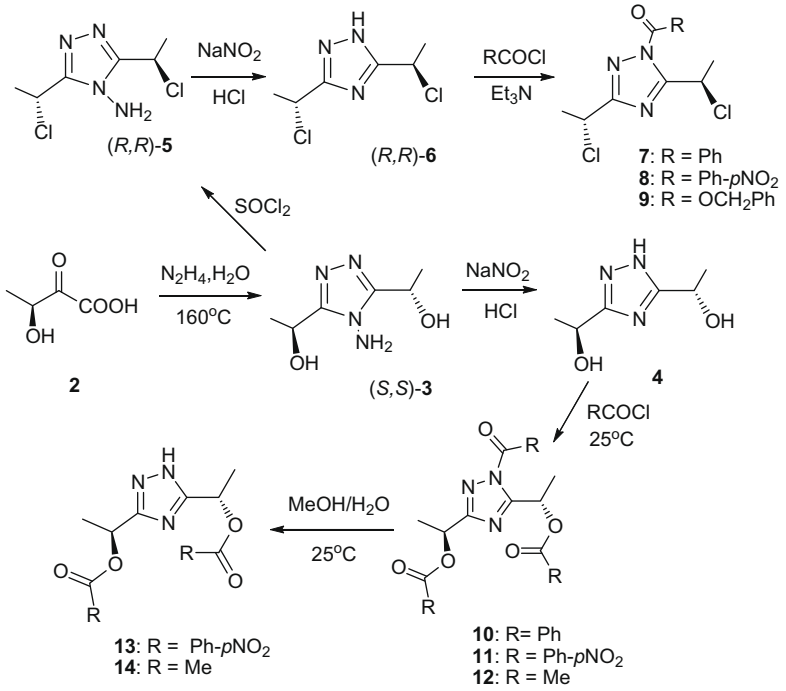
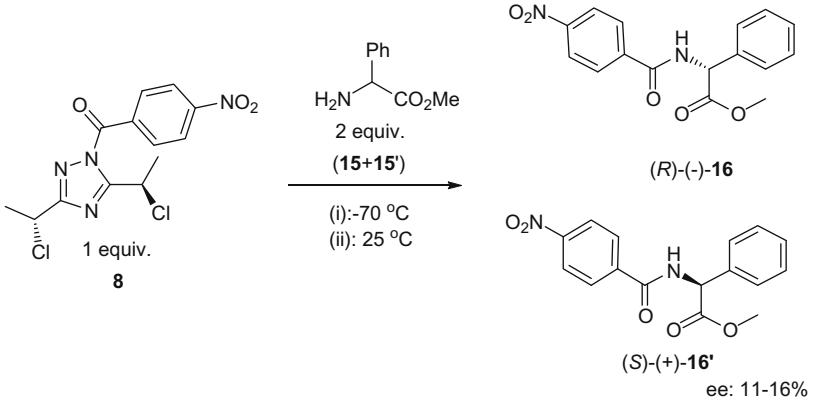


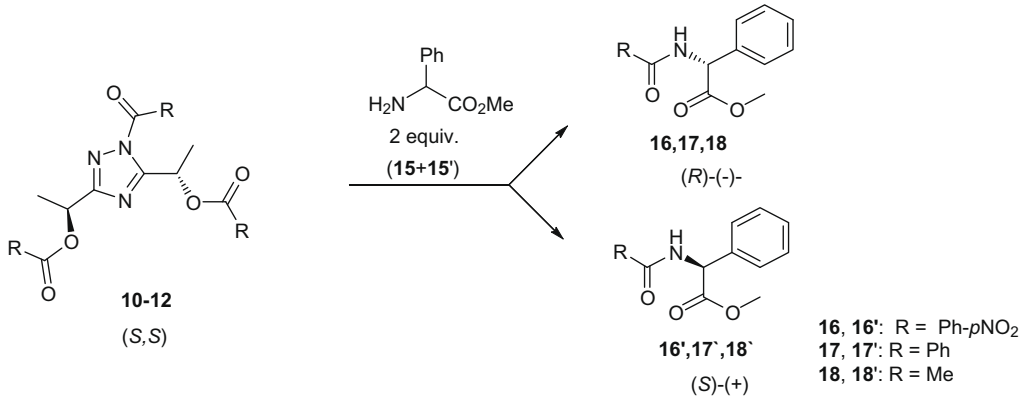
Scheme 1.



Scheme 2. Synthesis of chiral acylation reagents **7**–**12**.



Scheme 3.



Scheme 4.

Table 1
Results for the acylation of racemic phenylglycine methyl ester with **8**, **10**, **11**, and **12** under different conditions

Reagent/product	Yield[a] (%)	Reaction conditions		$[\alpha]_D^{23}$[b]	Enantiomeric excess, ee % (*S*/*R*)	Enantiomeric ratio, er (*S*/*R*)
		Temperature (°C)	Time (h)			
8/(**16**+**16**′)	87	−70 to +15	5	−7	ee = 11.4[c,d]	er = 1.26
10/(**17**+**17**′)	78	+25	1	+23.4	ee = 67.6	er = 5.18
	56	−70	6	+5.6	ee = 51.5	er = 3.12
11/(**16**+**16**′)	73	+25	1	+7	ee = 11.4	er = 1.26
	77	−60 to −10	2	+20	ee = 32.5	er = 1.96
		−10 to +15	8			
	37	−70 (−70 to +15)	40 (8)	+34	ee = 55.3	er = 3.47
12/(**18**+**18**′)	72	+25	1	−36.0	ee = 23.6[c,d]	er = 1.61
	48	−70	6	−2.35	ee = 6.79[c,d]	er = 1.14

[a] Isolated yield.
[b] Specific rotations were measured in CH_2Cl_2, $c = 2$.
[c] *R*/*S*.
[d] Specific rotation was measured for $c = 1$, CH_2Cl_2.

Chiral acylated triazoles (*R*,*R*)-**8** and (*S*,*S*)-**10**, (*S*,*S*)-**11**, and (*S*,*S*)-**12** were studied for the stereoselectivity in acyl group transfer to the NH_2 group of racemic phenylglycine methyl ester (**15**+**15**′) under different reaction conditions (Scheme 3). Compound **8** showed stereoselectivity and formed an optically active mixture (**16**+**16**′)[†] with 16% (*S*) isomer excess according to HPLC data and 11% excess according to specific rotation measurement: −7.0 (*c* 1, CH_2Cl_2). Compound **11** when reacted with racemic (**15**+**15**′) also acylated the L-phenylglycine methyl ester **15**′ isomer stereoselectively to give (Scheme 4) an enantiomeric excess (ee) of **16**′ which increased from 11% at 25 °C to 55% at −70 °C.

Results of the reactions were analyzed by the specific rotation and HPLC. For this purpose, optically pure enantiomers **16**, **17**, **18** and **16**′, **17**′, **18**′ were prepared as standards by acylating commercial (*R*) and (*S*)-phenylglycine methyl esters with the appropriate acyl chlorides. Enantiomeric excesses were calculated for the resulting mixtures obtained in different reaction conditions by measuring the specific rotations of pure **16**, **16**′, **17**, **17**′, **18**, **18**′, and the products isolated after reaction, considering that the contribution of each component of the mixture to the total specific rotation was directly proportional to its molar fraction. The experimental data for the acylation of **8, 10**, **11**, and **12** are presented in Table 1.

Increasing the substituent size near the stereogenic center increased chiral induction at 25 °C from 11.4% ee to 67.6% ee favoring from (*R*)- to (*S*)-isomer excess. We believe that another substituent at the stereogenic center could further increase the selectivity of a chiral 1,2,4-triazole.

2.1. Unexpected inversion of configuration

The reaction of (*S*,*S*)-**3** with thionyl chloride afforded (*R*,*R*)-**5** as a major product in 58% (isolated yield), in which both stereogenic centers had been inverted. The stereochemistry of (*R*,*R*)-**5** was confirmed by X-ray analysis (Fig. 1). This result was unexpected as it contradicts the literature report[25] that the (*S*,*S*) stereoisomer (69%) is the major product. The other product from our reaction of (*S*,*S*)-**3** with $SOCl_2$ was analyzed; based on the specific rotation values, ^{1}H NMR spectra, HPLC, and HRMS we concluded that the other stereoisomer of the reaction was the *meso* diastereoisomer of (*S*,*R*)-**5**′, which was also produced in a 1:12 mixture with the

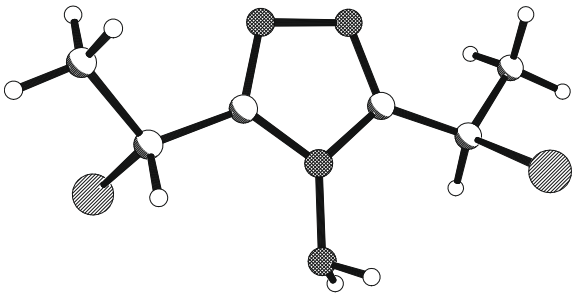
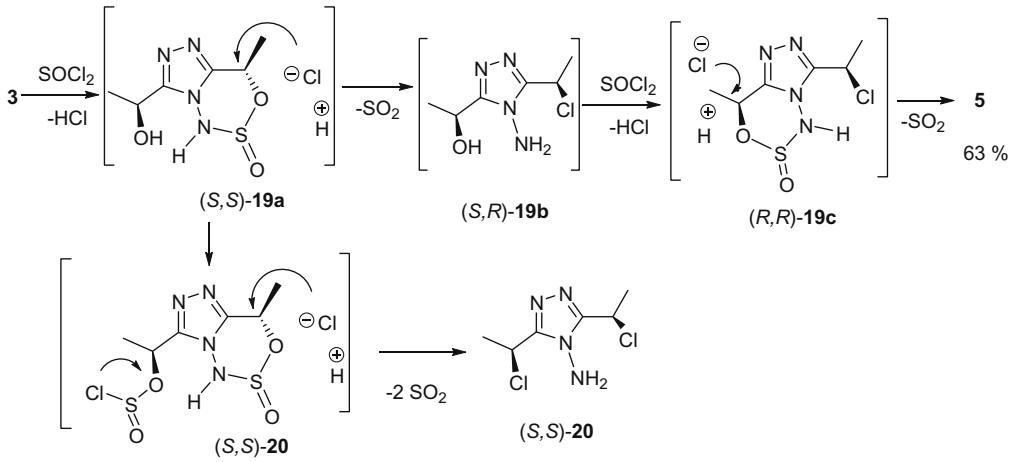


Figure 1. X-ray structure of 4-amino-3,5-bis(*R*-1-chloroethyl)-1,2,4-triazole, (*R*,*R*)-**5**.

[†] Compound numbers written within brackets represent a racemate or a diastereomeric mixture; compound numbers without brackets represent a single enantiomer.



Scheme 5. Suggested mechanism for the formation of triazoles (*R,R*)-**5** and (*S,R*)-**5′**.

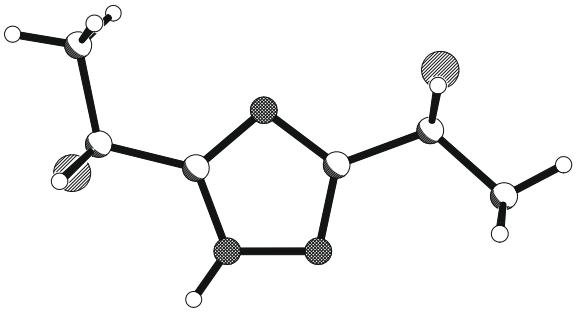


Figure 2. X-ray structure of 3,5-bis-((*R*)-1-chloro-ethyl)-1*H*-[1,2,4]triazole **6**.

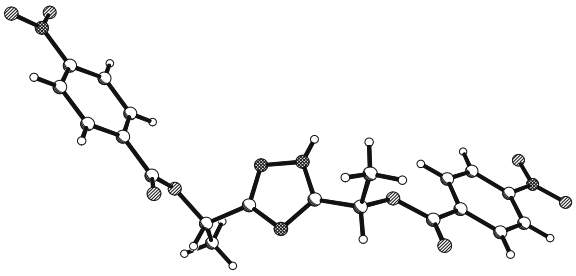
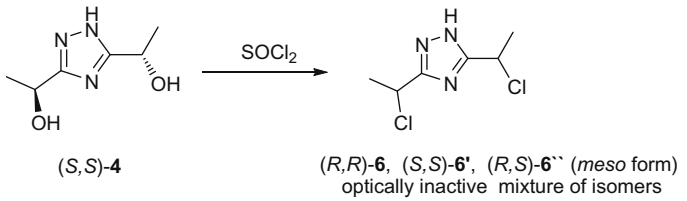


Figure 3. X-ray structure of 1-[5-(1-4-nitrobenzoyloxy-ethyl)-2*H*-1,2,4-triazol-3-yl]-ethyl 4-nitrobenzoate **13**.

(*R,R*)-**5** (Scheme 5). The structures of **6** and **13** were also confirmed by X-ray analysis (Figs. 2 and 3). Our suggested mechanism for the predominant formation of (*R,R*)-**5** involves the cyclic intermediates **19a** and **19c** formed by cyclization of the amino and hydroxy groups with thionyl chloride (Scheme 5).



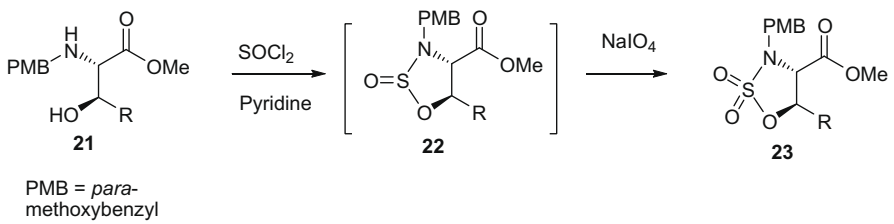
Scheme 6.

To support our suggestion of the decisive involvement of the amino group in the highly stereoselective conversion of (*S,S*)-**3** to (*R,R*)-**5**, we demonstrated that **4** was converted by thionyl chloride into an optically inactive mixture of several stereoisomers, presumably consisting of (*R,R*)-**6**, (*S,S*)-**6′**, and (*R,S*)-**6″** (Scheme 6).

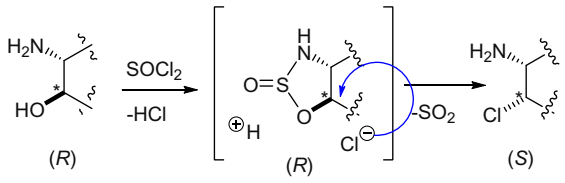
The strong influence of the amino group on the conversion of (*S,S*)-**3** to (*R,R*)-**5** may reflect a more general existence of control by a β-amino group to direct the substitution of an OH group mediated by thionyl chloride towards inversion. This issue requires further investigation, but a literature search revealed[26] a cyclic intermediate similar to **19a,c** supporting our hypothesis (Scheme 7). Substitution of the β-OH group in amino acid **21** (Scheme 7) with thionyl chloride in the presence of pyridine favored cyclic intermediate **22**, which was isolated (but not characterized), and oxidized to cyclic sulfamidate **23**.[26]

Thus the stereoselective substitution of a hydroxyl group with thionyl chloride managed by a β-amino group could be a general phenomenon, available for the synthesis of chiral chlorides (Scheme 8).

Single crystal X-ray structure determinations were carried out for **5**, **6**, and **13**, which unambiguously confirmed the relative configurations of all three compounds and the absolute configurations of **5** and **6**, due to the anomalous dispersion of the chlorine atoms.



Scheme 7.



Scheme 8.

Both compounds **5** and **6** crystallize with more than one molecule in the asymmetric unit (i.e., $Z' > 1$). The aminotriazole **5** crystallizes in the orthorhombic space group $P2_12_12_1$ with $Z' = 3$ and all three independent molecules have similar conformations. The triazole **6** crystallizes in the monoclinic space group $P2_1$ with $Z' = 4$. The fact that these four molecules are truly independent is supported by the fact that they have different conformations, with Cl–C–C–N3 torsional angles varying between 50.1° and 161.8°. A search of the Cambridge Structural Database[27] showed that only 0.40% and 0.37% of structures have $Z' = 3$ and 4, respectively. There has been much discussion, indeed controversy, about the possible reasons for high Z' values.[28–31] In the solid state both these compounds are packed with extensive intermolecular hydrogen bonds.

3. Conclusion

Chiral 1,2,4-triazoles are promising reagents for chiral acylation; we have achieved an enantiomeric excess of 67.6% for triazole **10**. The synthesis of triazole **5** revealed the stereospecific control of the amino group on substitution of a beta hydroxy group with thionyl chloride to give chiral triazoles **5** and **6** with unusual crystal structures.

4. Experimental

4.1. General methods

Melting points were determined on a capillary melting point apparatus equipped with a digital thermometer. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with TMS for ^1H (300 MHz) and ^{13}C (75 MHz) as the internal reference. Elemental analyses were performed on a Carlo Erba-1106 instrument. Optical rotation values were measured at the sodium D line. HPLC analyses were performed on Shimadzu LC solution programmable solvent module LC-20AT using (*S*,*S*) Whelk O1 column (25 cm × 4.6 mm), detection at 215 nm, flow rate of 1 mL/min, and isopropanol/hexanes as an eluting solvent.

(*R*)- and (*S*)-Methyl 2-benzamido-2-phenylacetate **17**, **17′**,[20] and (*R*)- and (*S*)-methyl 2-(acetylamino)-2-phenylacetate **18**, **18′**[32] were prepared by the literature procedures, respectively, as standard compound for HPLC analysis. All analytical data matched literature values.

4.2. X-ray crystallography

Crystal data and experimental details of the data collections and structure refinements are listed in Table 2. Data were collected with a APEX II CCD area detector, using graphite monochromatized Mo Kα radiation ($\lambda = 0.71073$ Å). The structures were solved by direct methods using SHELXS,[33] and refined on F^2 using all data by full-matrix least-squares procedures with SHELXL-97.[34]

Hydrogen atoms were included in calculated positions with isotropic displacement parameters 1.3 times the isotropic equivalent of their carrier atoms. Crystallographic data, as CIF files, have been deposited with the Cambridge Crystallographic Data Centre (CCDC Nos. 701228–701230). Copies can be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (e-mail: deposit@ccdc.cam.ac.uk).

4.3. General procedure for chiral acylation (for triazole 8)

To a solution of the racemate of phenylglycine methyl ester hydrochloride (0.16 g, 0.80 mmol) in THF (10 mL) was added triethylamine (0.11 mL, 0.80 mmol) at room temperature and the reaction mixture was stirred and cooled to −70 °C. Then [3,5-bis-((*R*)-1-chloro-ethyl)-[1,2,4]triazol-1-yl]-(4-nitrophenyl)-methanone **8** (0.14 g, 0.40 mmol) in THF (2 mL) was added dropwise over 5 min and the reaction mixture was stirred in a cooling bath (dry ice and isopropanol) for 5 h with gradual increasing temperature from −70 °C to +15 °C. Next, THF was evaporated under reduced pressure; the product was extracted with dichloromethane (50 mL), and filtered. The organic solution was washed with 4 N

Table 2
Crystal data and X-ray experimental details for compounds **5**, **6**, and **13**

Compound	**5**	**6**	**13**
Empirical formula	$C_6H_{10}N_4Cl_2$	$C_6H_9N_3Cl_2$	$C_{20}H_{17}N_5O_8$
Formula weight	209.08	194.06	455.39
Crystal system	Orthorhombic	Monoclinic	Monoclinic
Space group	$P2_12_12_1$	$P2_1$	$P2_1$
Unit cell dimensions			
a (Å)	9.8480(4)	9.0178(2)	5.0789(5)
b (Å)	15.8197(6)	9.8706(2)	22.316(3)
c (Å)	17.5827(7)	20.1658(5)	9.2116(10)
β (°)	90	91.585(2)	93.527(5)
Volume (Å^3)	2739.3(2)	1794.29(7)	1042.1(2)
Z	12	8	2
Density (calculated) (Mg/m^3)	1.521	1.437	1.451
Absorption coefficient (mm^{-1})	0.661	0.664	0.115
F(0 0 0)	1296	800	472
Crystal size (mm^3)	0.65 × 0.12 × 0.11	0.64 × 0.21 × 0.15	0.45 × 0.34 × 0.33
Theta range for data collection (°)	2.32–30.0	2.02–27.50	2.22–25.04
Reflections collected	73,661	27,991	3457
Independent reflections [R(int)]	7991 [0.0398]	8231 [0.0348]	2471 [0.0479]
Observed reflections [$I > 2\sigma(I)$]	7609	7550	2318
Data/restraints/parameters	7991/0/349	8231/1/397	2471/1/302
Goodness-of-fit on F^2	1.034	1.017	1.050
R_1 [$I > 2\sigma(I)$]	0.0241	0.0404	0.0462
wR_2 (all data)	0.0611	0.1103	0.1430

HCl, dried over Na_2SO_4, and dichloromethane was removed under reduced pressure to give methyl (*R/S*)-(4-nitrobenzoylamino)phenylacetate (**16**+**16′**) (0.11 g, 87%): mp 198–199 °C; $[\alpha]_D^{25} = -7.0$ (*c* 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 3H), 5.75 (d, *J* = 7.0 Hz, 1H), 7.27 (d, *J* = 7.0 Hz, 1H), 7.35–7.48 (m, 5H), 7.97 (d, *J* = 8.8 Hz, 2H,), 8.27 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR($CDCl_3$) δ 53.1, 57.0, 123.8, 127.3, 128.4, 128.9, 129.2, 135.9, 139.0, 149.8, 164.5, 171.2. (4-Nitrobenzoylamino)phenylacetate (**16**+**16′**) is a true racemate with melting point higher than the pure enantiomers.

4.4. (*S,S*)-3,5-Bis(1-hydroxyethyl)-1,2,4-triazole 4[25]

A solution of sodium nitrite (1.93 g, 28 mmol) in water (30 mL) was added dropwise to a stirred and cooled solution (0 °C) of **3** (3.44 g, 20 mol) in 6 M HCl (20 mL). The temperature was kept below 5 °C during the addition. After an additional 1 h under stirring, the solution was neutralized with saturated sodium bicarbonate to pH∼7, and then the solvent was removed under reduced pressure. The residue was extracted with hot acetonitrile and filtered. Evaporation of solvent gave compound **4** (2.98 g, 95%): mp 133–134 °C (crystallized from acetonitrile) (lit.[25] mp 134 °C); ^{1}H NMR (DMSO-d_6) δ 1.39 (d, *J* = 6.6 Hz, 6H), 4.74 (q, *J* = 6.6 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 22.7, 62.4, 163.0.

4.5. (*R,R*)-4-Amino-3,5-bis(1-chloroethyl)-1,2,4-triazole 5[25]

A mixture of **3** (3.00 g, 17 mmol) and thionyl chloride (5 mL) was stirred at 50–70 °C for 2 h. The excess reagent was removed in vacuo, after which the residue was dissolved in water (5 mL), neutralized with saturated sodium bicarbonate (up to pH 8), and extracted with dichloromethane. The resulting organic layer was dried over Na_2SO_4 and evaporated to give a mixture of diastereoisomers **5** (2.41 g, 73%, *RR*/*RS* = 12:1). The pure (*RR*)-isomer of **5** was obtained by recrystallization from a mixture of methanol, dichloromethane, and hexane as a white solid. (2.06 g, 58%): mp 145–147 °C (lit.[25] mp 145 °C); $[\alpha]_D^{25} = -216.5$ (*c* 2, CH_2Cl_2) (lit. $[\alpha]_D^{25} = -189.5$ (*c* 1.5, ethanol)); ^{1}H NMR (DMSO-d_6) δ 1.91 (d, *J* = 6.7 Hz, 6H), 5.46 (q, *J* = 6.7 Hz, 2H), 6.0 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 21.9, 46.0, 155.1. Pure (*RR*)-**5** precipitated during neutralization and can be isolated by simple filtration with the yield up to 50%.

4.6. 3,5-Bis-((*R*)-1-chloroethyl)-1*H*-[1,2,4]triazole 6

A solution of sodium nitrite (0.19 g, 2.80 mmol) in water (2 mL) was added dropwise to a stirred and cooled solution (0 °C) of **5** (0.42 g, 2 mmol) in 6 M HCl (4 mL). The temperature was kept at 0–5 °C during the addition and the reaction mixture was stirred overnight. The resulting solution was neutralized with saturated sodium bicarbonate to pH ∼7 and was extracted with dichloromethane. The organic layer was separated, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by recrystallization from a mixture of acetone/hexanes to give pure compound **6** (0.27 g, 70%): mp 127–128 °C; $[\alpha]_D^{25} = +52$ (*c* 2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.93 (d, *J* = 7.0 Hz, 6H), 5.21 (q, *J* = 7 Hz, 2H), 12.29 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 23.8, 23.9, 49.4, 161.2. Anal. Cald for $C_6H_9Cl_2N_3$: C, 37.14; H, 4.67; N, 21.65. Found: C,37.24; H, 4.63; N, 21.58.

4.7. [3,5-Bis(1-chloroethyl)-[1,2,4]triazol-1-yl]-phenyl-methanone 7 as a mixture of stereoisomers

A mixture of **6** (0.20 g, 1 mmol), benzoyl chloride (0.14 g, 1 mmol), and triethylamine (0.10 g, 1 mmol) in THF (10 mL) was stirred at room temperature for 6 h. Precipitated triethylamine hydrochloride was removed by filtration, the organic solution was evaporated, and the residue was purified by flash silica gel chromatography (eluent: dichloromethane) to give **7** (0.19 g, 66%): mp 80–84 °C; ^{1}H NMR ($CDCl_3$) δ 1.92 (d, *J* = 7.0 Hz, 1.5H), 1.94 (d, *J* = 6.9 Hz, 1.5H), 2.05 (d, *J* = 6.9 Hz, 3H), 5.12–5.20 (m, 1H), 5.82–5.90 (m, 1H), 7.53 (t, *J* = 8.0 Hz, 2H), 7.68 (t, *J* = 7.6 Hz, 1.6H), 8.14–8.19 (m, 0.4H); ^{13}C NMR ($CDCl_3$) δ 22.6, 23.0, 23.1, 47.6, 47.6, 49.6, 128.4, 128.9, 130.5, 131.8, 131.8, 134.3, 134.5, 161.3, 163.4, 166.2. Anal. Calcd for $C_{13}H_{13}Cl_2N_3O$: C, 52.37; H, 4.39; N, 14.09. Found: C, 52.74; H, 4.56; N, 13.93. Repetition of the synthesis with the procedure as for **8** (fast procedure) gave the same racemic product.

4.8. [3,5-Bis-((*R*)-1-chloroethyl)-[1,2,4]triazol-1-yl]-(4-nitrophenyl)-methanone 8

To a solution of **6** (0.40 g, 2 mmol) and 0.37 g (2 mmol) of 4-nitrobenzoyl chloride (0.37 g, 2 mmol) in dichloromethane (10 mL) was added dropwise a solution of triethylamine (0.20 g, 2 mmol) in dichloromethane (5 mL) at room temperature for 2–3 min. After 0.5 h, precipitated triethylamine hydrochloride was removed by filtration, the organic solution was evaporated, and the residue was purified by flash silica gel chromatography (eluent: dichloromethane) to give **8** (0.41 g, 59%): mp 75–76 °C; racemate mp = 118–121 °C (racemate was obtained from the starting *RS* lactic acid); $[\alpha]_D^{25} = -112$ (*c* 2, CHC_{l3}), other sample $[\alpha]_D^{25} = -198$ (*c* = 2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.93 (d, *J* = 6.9 Hz, 3H), 2.07 (d, *J* = 6.9 Hz, 3H), 5.14 (q, *J* = 6.9 Hz, 1H), 5.86 (q, *J* = 6.9 Hz, 1H), 8.24 (d, *J* = 9.1 Hz, 2H, A part of AB system), 8.38 (d, *J* = 9.1 Hz, 2H, B part of AB system); ^{13}C NMR ($CDCl_3$) δ 22.4, 23.0, 47.6, 49.3, 123.3, 132.6, 136.1, 150.6, 161.7, 164.0, 164.5 Anal. Calcd for $C_{13}H_{12}Cl_2N_4O_3$: C, 45.50; H, 3.52; N, 16.33. Found: C, 45.29; H, 3.63; N, 16.01.

4.9. 3,5-Bis-(1-chloroethyl)-[1,2,4]triazole-1-carboxylic acid benzyl ester 9 as a mixture of stereoisomers

A mixture of **6** (0.20 g, 1 mmol), benzyl chloroformate (0.17 g, 1 mmol), and triethylamine (0.10 g, 1 mmol) in THF (10 mL) was stirred at room temperature for 6 h. Precipitated triethylamine hydrochloride was removed by filtration and the organic solution was evaporated. The residue was purified by flash silica gel chromatography (eluent: dichloromethane/hexanes = 1:1) to give **9** (0.18 g, 55%): pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.91 (d, *J* = 6.9 Hz, 3H), 1.97 (d, *J* = 6.9 Hz, 1.5 H), 1.98 (d, *J* = 6.9 Hz, 1.5 H), 5.08–5.22 (m, 1H), 5.51 (s, 2H), 5.75 (q, *J* = 6.9 Hz, 1H), 7.30–7.56 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.5, 23.0, 23.1, 47.0, 47.1, 49.4, 71.0, 128.8, 129.1, 129.3, 133.4, 148.0, 160.7, 164.0. Anal. Calcd for $C_{14}H_{15}Cl_2N_3O$: C, 51.24; H, 4.61; N, 12.80. Found: C, 52.19; H, 4.82; N, 12.45. Repetition of the synthesis with the procedure as for **8** (fast procedure) gave the same racemic product.

4.10. (1*S*,1′*S*)-1,1′-(1-Benzoyl-1*H*-1,2,4-triazole-3,5-diyl)-bis(ethane-1,1-diyl)dibenzoate 10

The mixture of **4** (0.31 g, 2 mmol), benzoyl chloride (0.84 g, 6 mmol), and triethylamine (0.60 g, 6 mmol) in THF (10 mL) was stirred at room temperature for 12 h and was filtered to remove triethylamine hydrochloride. The resulting solution was evaporated under reduced pressure and the residue was purified by flash silica gel chromatography (eluent: dichloromethane/hexanes = 1:1) or recrystallized from a mixture of dichloromethane and petroleum ether to give **10** (0.60 g, 63%): mp 57–60 °C; $[\alpha]_D^{25} = +66.84$ (*c* 2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.78 (d, *J* = 6.7 Hz, 3H), 1.91 (d, *J* = 6.7 Hz, 3H), 6.24 (q, *J* = 6.7 Hz, 1H), 6.63 (q, *J* = 6.7 Hz, 1H), 7.32–7.46 (m, 6H), 7.49–7.64 (m, 3H), 7.98–8.11 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 18.7, 19.1, 65.9, 66.7, 128.1, 128.2, 128.3, 129.4, 129.7, 129.8, 129.9, 130.6, 131.9, 133.0, 133.1, 134.0, 161.1, 162.8, 165.7, 165.8, 166.1. Anal. Calcd for $C_{54}H_{48}N_6O_{11}\cdot\frac{1}{2}H_2O$: C, 67.77; H, 5.06; N, 8.78. Found: C, 67.38; H, 4.70; N, 8.44.

4.11. (1*S*,1′*S*)-1,1′-[(1-(*p*-Nitrobenzoyl)-1*H*-1,2,4-triazole-3,5-diyl)]-bis(ethane-1,1-diyl)-bis(*p*-nitro- benzoate) 11

A mixture of **4** (0.31 g, 2 mmol), *p*-nitrobenzoyl chloride (1.11 g, 6 mmol), and triethylamine (0.60 g, 6 mmol) in THF (10 mL) was stirred at room temperature for 12 h and was filtered to remove triethylamine hydrochloride. The resulting solution was evaporated under reduced pressure and the residue was purified by flash silica gel chromatography (eluent: dichloromethane/hexanes = 1:1) to give **11** (0.60 g, 50%). Crystallization from a mixture of dichloromethane/petroleum ether by freezing gave the product with mp = 57–60 °C. Further purification by column chromatography (eluent: dichloromethane) gave the product: mp 67–70 °C; $[\alpha]_D^{25} = +87.5$ (*c* 2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 1.79 (d, *J* = 6.7 Hz, 3H), 1.93 (d, *J* = 6.6 Hz, 3H), 6.23 (q, *J* = 6.7 Hz, 1H), 6.63 (q, *J* = 6.6 Hz, 1H), 8.17–8.31 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 18.5, 18.8, 66.8, 67.4, 123.2, 123.5, 123.6, 130.8, 130.9, 132.7, 134.8, 135.0, 135.9, 150.7, 150.8, 161.3, 163.2, 163.9, 164.1, 164.5. Anal. Calcd for $C_{27}H_{20}N_6O_{11}$: C, 53.65; H, 3.33; N, 13.90. Found: C, 53.74; H, 3.23; N, 13.52.

4.12. (1*S*,1′*S*)-1,1′-(1-Acetyl-1*H*-1,2,4-triazole-3,5-diyl)-bis(ethane-1,1-diyl)diacetate 12

A solution of acetic anhydride (22 g, 21 mmol) and **4** (1.60 g, 10 mmol) was mixed at room temperature, then potassium carbonate (0.14 g, 1 mmol) in water (2 mL) was added. The mixture was kept under stirring for 2 h at the same condition, was evaporated until dry, then dissolved with dichloromethane (30 mL); washed with water (20 mL) twice, then with brine (20 mL) twice. The organic layer was further dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was dried in vacuo to yield **12** (2.15 g, 76%): colorless oil; $[\alpha]_D^{25} = -131.9$ (*c* 2, CH_2Cl_2). ^{1}H NMR (DMSO-d_6) δ 1.54 (d, *J* = 6.6 Hz, 6H), 2.05 (d, *J* = 9.0 Hz, 6H), 2.65 (s, 3H), 5.86 (q, *J* = 6.6 Hz, 1H), 6.23 (q, *J* = 6.6 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 17.9, 18.8, 19.1, 20.5, 20.8, 20.9, 23.5, 64.9, 65.3, 158.9, 161.8, 169.5. Anal. Calcd for $C_{12}H_{17}N_3O_5$: C, 50.88; H, 6.05; N, 14.83. Found: C, 50.68; H, 5.69; N, 15.24.

4.13. 4-Nitrobenzoic acid 1-[5-(1-4-nitrobenzoyloxy-ethyl)-2*H*-1,2,4-triazol-3-yl]-ethyl ester 13

The second product isolated during column separation of **11** was pure solid **13** (0.20 g, 22%): mp 173–178 °C; $[\alpha]_D^{25} = +36.6$ (*c* 2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.87 (d, *J* = 6.7 Hz, 6H), 6.28 (q, *J* = 6.7 Hz, 2H), 8.17–8.30 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 18.8, 66.8, 123.6, 131.0, 134.8, 150.7, 159.2, 164.4 Anal. Calcd for $C_{20}H_{17}N_5O_8$): C, 52.75; H, 3.76; N, 15.38. Found: C, 52.69; H, 3.85; N, 14.76.

4.14. (1*S*,1′*S*)-1,1′-(1*H*-1,2,4-Triazole-3,5-diyl)-bis-(ethane-1,1-diyl) diacetate 14

Compound **12** (2.80 g, 10 mmol) was stirred in water (7.2 mL) at room temperature for 12 h. The resulting solution was evaporated under reduced pressure, then dried in vacuo for 24 h to yield **14** (2.29 g, 95%): colorless oil; $[\alpha]_D^{25} = -156$ (*c* 2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.68 (d, *J* = 6.6 Hz, 6H), 2.10 (s, 6H), 6.02 (q, *J* = 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 19.9, 21.0, 65.4, 159.6, 170.6. Anal. Calcd for $C_{20}H_{32}N_6O_{9}\cdot\frac{1}{2}H_2O$: C, 48.0; H, 6.44; N, 16.79. Found: C, 47.72; H,6.50; N, 16.66.

4.15. Methyl (*S*)-(4-nitro-benzoylamino)phenylacetate 16′

A mixture of (*S*)-phenylglycine methyl ester hydrochloride (0.20 g, 1 mmol), *p*-nitrobenzoyl chloride (0.18 g, 1 mmol), and triethylamine (0.20 g, 2 mmol) in THF (10 mL) was stirred at room temperature for 12 h. THF was removed under vacuum at room temperature, the residue was extracted with dichloromethane (30 mL x 2) which was washed with water and evaporated in vacuo at room temperature to give **16′** (0.28 g, 90%). The product was then recrystallized from a mixture of dichloromethane and hexanes by freezing to give white crystals (0.28 g, 90%): mp = 189–191 °C; $[\alpha]_D^{25} = +61.5$ (*c* = 2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 3H), 5.75 (d, *J* = 6.9 Hz, 1H), 7.29 (d, *J* = 6.9 Hz, 1H), 7.35–7.48 (m, 5H), 7.97 (d, *J* = 8.9 Hz, 2H), 8.27 (d, *J* = 8.9 Hz, 2H); ^{13}C ($CDCl_3$) δ 53.1, 57.0, 123.8, 127.3, 128.4, 128.9, 129.1, 135.9, 139.0, 149.7, 164.5, 171.2. Anal. Calcd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found: C, 60.95; H, 4.43; N, 8.76.

4.16. Methyl (*R*)-(4-nitro-benzoylamino)phenylacetate 16

This enantiomer was prepared by the same procedure as **16′** (0.29 g, 94%); mp 190–191 °C; $[\alpha]_D^{25} = -62.7$ (*c* 2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 3H), 5.75 (d, *J* = 7.0 Hz, 1H), 7.27 (d, *J* = 7.0 Hz, 1H), 7.35–7.48 (m, 5H), 7.97 (d, *J* = 8.8 Hz, 2H,), 8.27 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR($CDCl_3$) δ 53.1, 57.0, 123.8, 127.3, 128.4, 128.9, 129.2, 135.9, 139.0, 149.8, 164.5, 171.2. Anal. Calcd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found: C, 60.98; H, 4.50; N, 8.80.

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