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Preparation and Enantiomeric Purity Determination of New Chiral C_2 Building Blocks Based on the 4-Amino-1,2,4-triazole Unit

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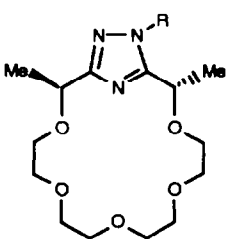
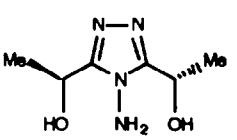
Abstract: Several new chiral synthons based on the 4-amino-1,2,4-triazole moiety have been prepared by the condensation reaction of optically active α-hydroxy- and α-aminoacids with hydrazine. A general method for the determination of the optical purity of chiral 4-amino-3,5-disubstituted-1,2,4-triazoles based on their oxidation with lead tetraacetate (LTA) is described.

There has been recent interest in macrocyclic compounds containing proton ionizable functional groups directly incorporated into a macrocyclic framework.[1] In this regard, 1,2,4-triazole subunits have been used extensively as building blocks for macrocyclic systems mainly by Bradshaw and coworkers[2-5] and by ourselves.[6-11] Recently, we have reported on the synthesis, complexation and protonated amine transport properties of chiral crown ether macrocycles such us **1**[8-10] and podands,[11] incorporating a 1,2,4-triazole moiety. In these cases, (*S,S*)-4-amino-3,5-bis-(1-hydroxyethyl)-1,2,4-triazole **2**[8], prepared by treatment of (*S*)-lactic acid or some of its derivatives with hydrazine, was used as a chiral precursor for the preparation of the triazolic macrocycles. The modest selectivities found in the enantiomeric recognition of organic ammonium salts by receptors **1**[9,10] are probably due to the low chiral barrier provided by the two chiral centers. In order to develop new systems having bulkier chiral substituents in a more rigid framework, we decided to prepare other 1,2,4-triazolic building blocks with C_2 symmetry[12] related to **2** derived from α-hydroxy acids, such as phenyllactic and mandelic acids, or natural α-aminoacids.

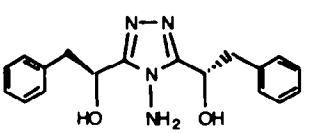


1

R = H , $C_{12}H_{25}$, $CH_2COcholesteryl$

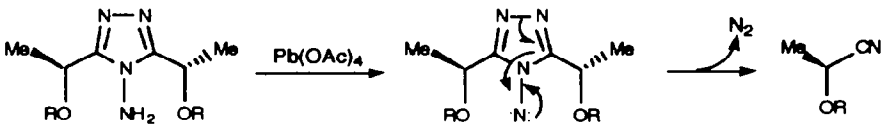


(*S,S*)-**2**



(*S,S*)-**3**

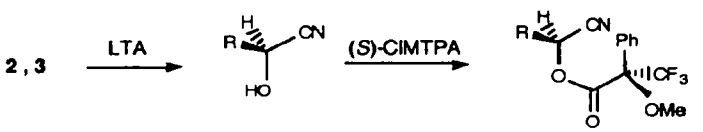
The condensation of (*S*)-phenyllactic acid with hydrazine under similar reaction conditions employed for the preparation of (*S,S*)-**2** afforded the corresponding triazole (*S,S*)-**3** in good yield (63 %). This compound, $[\alpha]_D$ = - 54.4 (*c* = 0.5, HCl 2 N), was shown to be a single diastereoisomer according to the ^{1}H- and ^{13}C-NMR data. Attempts to check the enantiomeric purity of (*S,S*)-**3** by means of its bis-(*S*)-α-methoxy-α-trifluoromethylphenyl-O-acetyl (MTPA) derivative were unsuccessful, probably due to the presence of three reactive functions in the substrate. This method, previously used by us[8] in the determination of the enantiomeric purity of triazole (*S,S*)-**2**, is not always unequivocal in this series of compounds and largely depends on the availability of both antipodes or their racemic mixture. For this reason it was necessary to develop a general procedure to establish the enantiomeric purity of chiral 4-amino-3,5-disubstituted-1,2,4-triazoles. Not long ago,[13] we observed that a chiral (*S,S*)-4-amino-3,5-disubstituted-1,2,4-triazole (Scheme 1), having stereogenic centers directly bound to the triazole ring, fragments on oxidation with lead tetraacetate (LTA), *via* the corresponding nitrene intermediate, to afford an optically active nitrile with the same configuration. Under these conditions racemization does not take place. Now, we have applied this reaction to analyse the enantiomeric purity of chiral 4-amino-1,2,4-triazoles.



R = COCH=CHPh

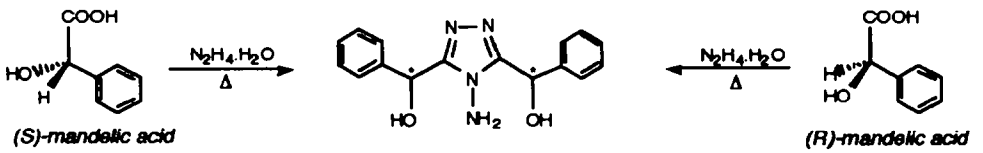
Scheme 1

Thus, treatment of (*S,S*)-**2** with LTA yields cyanhydrin (*S*)-**4** $[\alpha]_D$ = - 30 (*c* = 1, chloroform). Similarly, the (*R,R*)-**2** enantiomer $[\alpha]_D$ = - 31.5 (*c* = 1.5, H_2O) obtained by reaction of (*R*)-lactic acid with hydrazine hydrate affords the corresponding cyanhydrin (*R*)-**4**, $[\alpha]_D$ = + 30 (*c* = 1, chloroform). Reaction of (*S*)- and (*R*)-**4** with (*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPACl) afforded the corresponding MTPA derivatives clearly distinguishable by ^{1}H-NMR. Analysis of the spectra allows the enantiomeric purity to be assessed as higher than 98 % for both cyanhydrins **4** and, by chemical correlation, the same enantiomeric excess for their precursors (*S,S*)- and (*R,R*)-**2**. Similarly, compound (*S,S*)-**3** reacts with LTA affording (*S*)-**5**, $[\alpha]_D$ = - 10.6 (*c* = 1, chloroform) [Lit[14] (*R*)-**5**: $[\alpha]_D$ = + 10.5 (*c* = 1, chloroform)]. Comparison of the ^{1}H-NMR spectra of the MTPA derivatives of (*S*)-**5** and of the racemic cyanhydrin (*RS*)-**5**, obtained by addition of cyanhydric acid to 2-phenylacetaldehyde, reveals that the enantiomeric purity of (*S*)-**5**, and therefore of (*S,S*)-**3**, is also higher than 98 %.



(*S*)-**4** R = Me
(*S*)-**5** R = CH_2Ph

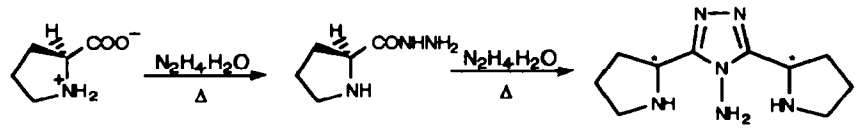
The reaction of (*S*)- and (*R*)-mandelic acids with hydrazine hydrate affords in both cases the same optically inactive mixture of *racemic* and *meso*-4-amino-3,5-bis-(1-phenyl-1-hydroxymethyl)-1,2,4-triazoles (*RS,RS*)-**6** and (*R,S*)-**6**. The relative higher acidity of the methyne protons in this case should be responsible for the epimerization and racemization processes.



(S)-mandelic acid *(R)-mandelic acid*

(RS,RS)-**6** + (*R,S*)-**6**

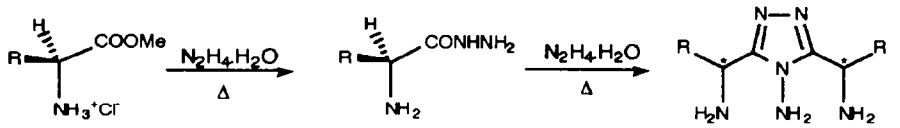
Only a few examples of condensation reactions of α-aminoacids with hydrazine to afford 1,2,4-triazoles have been described.[15] The reactivity of natural α-aminoacids with hydrazine hydrate, in comparison with those of the α-hydroxyacids described above, is significantly lower. Thus, L-alanine, L-phenylalanine and L-valine react slowly with hydrazine hydrate to afford, after prolonged heating (120 h) at 150 °C, oily mixtures of the corresponding triazole, the monohydrazide intermediate and even unreacted starting aminoacid in different ratios. Only with L-proline was it possible to isolate pure 4-amino-3,5-bis-(2-pyrrolidin)-1,2,4-triazole (**8**) which precipitates from the reaction mixture in 40 % yield after 72 h. heating at 150 °C. In this reaction, the prolinhydrazide **7** was also isolated as hydrochloride in 38 % yield. Compound **8** has a great interest because structurally rigid pyrrolidine derivatives often lead to very high asymmetric inductions in organic synthesis. However, the enantiomeric purity of compound **8** could not be determined by the LTA method due the impossibility of isolating the corresponding nitrile(s) from the reaction mixture. The use of Mosher's derivatives, chiral lanthanide reagents and HPLC analysis on a chiral phase were also unsuccessful in this case.



L-Proline **7** **8**

L-Alanine and L-phenylalanine methyl esters hydrochlorides react faster with hydrazine hydrate (48 h), thus allowing the preparation of the corresponding triazoles **10** and **12** in 82 % and 52 % yield, respectively. With lower reaction times, the reactions afforded also the corresponding hydrazides **9** and **11** as major products that can be isolated as hydrochlorides.

Treatment of **10** with LTA in methanol gave a mixture of (*S*)- and (*R*)-2-aminopropanenitriles **13a** and **13b** in a 65:35 ratio analyzed by ^{1}H-NMR of their MTPA derivatives, thus indicating an enantiomeric purity of 30 % for the triazol **10**. The same result was obtained in the analysis of the enantiomeric purity (26 %) of compound **12**. In this case, (*S*)- and (*R*)-2-amino-3-phenylpropanenitriles **14a** and **14b** were obtained in a 63:37 ratio. Similar enantiomeric excesses were observed for the triazoles obtained in the reaction of D-alanine and D-phenylalanine methyl esters with hydrazine.

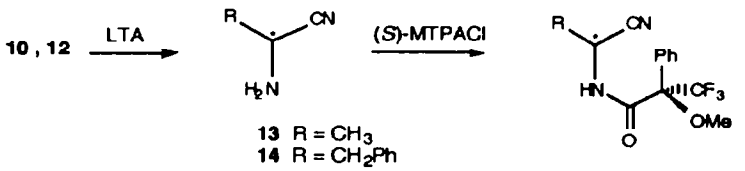


R = CH_3, CH_2Ph, $CH(CH_3)_2$

9 R = CH_3
11 R = CH_2Ph
15 R = $CH(CH_3)_2$

10 R = CH_3
12 R = CH_2Ph
16 R = $CH(CH_3)_2$

The condensation of the L-proline methyl ester with hydrazine hydrate gives triazole **7** in almost quantitative yield (^{1}H-NMR) after 48 h, but the compound does not precipitate from the reaction mixture. For this reason it is more convenient to prepare **7** from the free aminoacid as described before, despite the lower yield obtained. The reaction of L-valine methyl ester hydrochloride with hydrazine hydrate under the same reaction conditions is also faster than with the free aminoacid, but, even after 96 h, the corresponding triazole **16** is present only in a 40 % in the reaction mixture (^{1}H-NMR), the intermediate hydrazide **15** being the major component. From the data obtained in the reactions between α-hydroxy- and α-aminoacids with hydrazine hydrate it can be concluded that, the bulkier the substituents are in the α-position of the substrates, the more difficult the heterocyclization reaction is. The low solubility in common organic solvents and the hygroscopic character of the aminotriazoles derived from aminoacids hinder to a great extent the isolation and purification of the compounds.



13 R = CH_3
14 R = CH_2Ph

The contrast in the stereochemical behaviour of α-hydroxyacids (such as lactic and phenyllactic acids to give **2** and **3**) and related α-aminoacids (like alanine and phenylalanine to afford **9** and **11**) could be explained considering that the low reactivities of these substrates require the use of more drastic reaction conditions, in particular longer reaction times and higher excess of hydrazine. On the other hand, the lower acidity of the α-protons in compounds **2** and **3** should also play an important role in explaining the excellent enantiomeric excesses found in these cases.

In conclusion, we have confirmed that chiral building blocks based on the 4-amino-1,2,4-triazole unit can be prepared from α-alkyl-α-hydroxyacids in good yields and excellent (> 98 %) enantiomeric purities. On the other hand, α-alkyl-α-aminoacids afford moderate to good yields of the corresponding triazoles in low enantiomeric excesses (around 30 %). A general method to determine the enantiomeric purity of chiral 4-amino-3,5-disubstituted 1,2,4-triazoles of practical value as well as operational simplicity has been also developed.

Acknowledgements: Thanks are due to BASF Ludwigshafen (Germany) for a gift of (*R*)-lactic acid.

Experimental Section

General Procedure for the Preparation of 4-amino-3,5-bis-(1-hydroxyalkyl)- and (1-aminoalkyl)-1,2,4-triazoles. A well-stirred mixture of the corresponding α-hydroxyacid, α-aminoacid or α-aminoacid methyl ester hydrochloride and hydrazine hydrate was heated at 120 °C for 8 h. The excess of hydrazine and H_2O were distilled off while the temperature was raised up slowly to 160 °C and then the mixture was kept at this temperature for 5 h. The reaction was monitored by ^{1}H-NMR and the cycle -addition of hydrazine and heating- was repeated until the intermediate hydrazide disappeared. Finally, the reaction mixture was cooled down and worked up as indicated in each case.

(R,R)-4-amino-3,5-bis-(1-hydroxyethyl)-1,2,4-triazole **2**. From (*R*)-lactic acid (40 % in water solution, 53 g, 0.23 mol) and hydrazine hydrate (25 ml, 0.51 mol) a syrup was obtained which solidified on standing. Yield 56 % (acetonitrile); white solid; mp 128-30 °C; $[\alpha]_D$ = - 31.5 (c = 1.5, H_2O); [Lit[8] (*S,S*)-**2**: $[\alpha]_D$ = + 32 (c = 1.5, H_2O)]; ^{1}H-NMR (d_6-dmso): δ = 5.76 (s broad, 2H, NH_2), 5.39 (d, J=6.7 Hz, 2H, OH), 4.90 (q, J=6.7 Hz, 2H, CH), 1.47 ppm (d, J=6.7 Hz, 6H, CH_3).

(S,S)-4-amino-3,5-bis-(1-hydroxy-2-phenylethyl)-1,2,4-triazole **3**. From L-phenyllactic acid (2 g, 12 mmol) and hydrazine hydrate (10 ml, 0.2 mol), after two reaction cycles, triazole **3** precipitated as a white solid. Yield 63 % (acetonitrile); white needles; mp 220-2°C; $[\alpha]_D$ = - 54.4 (c = 0.5, HCl 2N); ^{1}H-NMR (d_6-dmso): δ = 7.3-7.1 (m, 10H, Ph), 5.7 (s, 2H, NH_2), 5.55 (d, 2H, J=6.5 Hz, OH), 4.93 (m, 2H, C<u>H</u>CH_2), 3.2 ppm (m, 2H, CH_2Ph); ^{13}C-NMR (d_6-dmso): δ = 155.7 (C-triazole), 138.6, 129.5, 128.0, 126.0 (arom), 64.5 (<u>C</u>HCH_2), 40.5 ppm (<u>C</u>H_2Ph); MS (FAB) *m/z* = 325 (M + H^+); Anal. Calcd for $C_{18}H_{20}N_4O_2$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.46; H, 6.19; N, 17.40.

(RS,RS)- and *(RS)-4-amino-3,5-bis-(1-hydroxy-1-phenylmethyl)-1,2,4-triazole* **6**. From L- or D-mandelic acid (0.5 g, 3.3 mmol) and hydrazine hydrate (5 ml, 0.1 mol), after two reaction cycles, a mixture of *racemic* and *meso*-triazoles **6** was obtained . Yield 60 % (acetonitrile); white needles; mp 218-20 °C; $[\alpha]_D$ = 0 (c = 0.5, HCl 2N); ^{1}H-NMR (d_6-dmso): δ = 7.5-7.2 (m, 10H, arom), 6.2 (m, 2H, OH), 5.95 (d, 2H, CH), 5.83 ppm (s, 2H, NH_2); ^{13}C-NMR (d_6-dmso): δ = 155.7, 155.6 (C-triazole), 141.3, 141.2, 127.9, 127.3, 126.8 (arom), 65.4 ppm (CH). MS (EI) *m/z* = 296 (M^+, 3), 279 (9), 262 (30), 260 (56), 259 (91); Anal Calcd for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44 ; N, 18.91. Found: C, 64.82; H, 5.36; N, 19.02.

4-amino-3,5-bis-(2-pyrrolidin)-1,2,4-triazole **8**. From L-Proline (5 g, 43 mmol) and hydrazine hydrate (100 ml, 2.1 mol), after five reaction cycles, compound **8** precipitated as a white solid. Yield 40% (acetonitrile); white hygroscopic solid; mp 129-31 °C; $[\alpha]_D$ = + 5.6 (c = 1, H_2O); ^{1}H-RMN (d_6-dmso): δ = 5.9 (s broad, 2H, NH_2), 4.24 (dd, 2H,CH), 2.8 (m, 4H, NCH_2), 2.2-1.6 ppm (m, 8H, CH_2); ^{13}C-RMN (d_6-dmso): δ = 155.9 (C-triazole), 52.2 (CH), 46.1 (NCH_2), 29.3, 25.4 ppm (CH_2); MS (FAB) *m/z* = 223 (M + H^+); Anal Calcd for $C_{10}H_{18}N_6$: C, 54.03; H, 8.16 ; N, 37.81. Found: C, 53.97; H, 8.12; N, 38.00.

4-amino-3,5-bis-(1-aminoethyl)-1,2,4-triazole **10**. From L- or D- alaninate methyl ester hydrochloride (1 g, 7 mmol) and hydrazine hydrate (17 ml, 0.35 mol), after four reaction cycles, a syrup was obtained. It was dried *in vacuo* and then treated with methanol (20 ml). The solution was filtered over Celite and the solvent was evaporated. Yield 82 %; oil; ^{1}H-RMN (d_6-dmso): δ = 6.2-5.8 (2 x s, NH_2), 4.08 (q, 2H, J=6.8 Hz, CH), 1.36 ppm (d, 6H, J=6.8 Hz, CH_3); ^{13}C-NMR (d_6-dmso): δ = 157.5 (C-triazole), 41.7 (CH), 21.1 ppm (CH_3); EM (high resolution, EI) *m/z* = Calcd for $C_6H_{14}N_6$: 170.1280. Found: 170.1279.

4-amino-3,5-bis-(1-amino-2-phenylethyl)-1,2,4-triazol **12**. From D-, L- or DL-phenylalanine methyl ester hydrochlorides (2 g, 9.3 mmol) and hydrazine hydrate (23 ml, 0.47 mol), after four reaction cycles, the

resulting precipitate was treated with sodium bicarbonate (0.2 g, 2.4 mmol) in acetonitrile (30 ml). The suspension was filtered over Celite and the residue was evaporated. Yield 52 % (ethyl acetate); white solid; mp 132-5 °C; $[\alpha]_D$ = + 5.2 (c = 1, MeOH) (from L-aminoacid); $[\alpha]_D$ = - 7.3 (c = 1, MeOH) (from D-aminoacid); ^{1}H-NMR (d_6-dmso): δ = 7.2 (m, 10H, arom), 5.9-5.8 (2 x s, NH_2), 4.2 (dd, 2H, CH), 3.1 ppm (m, 4H, CH_2); ^{13}C-NMR (d_6-dmso): δ = 156.8 (C-triazole), 139.0, 129.4, 128.0, 126.0 (arom), 48.2 (CH), 41.4 ppm (CH_2); MS *m/z* (relative intensity) 322 (M^+, 2), 307 (10), 289 (9), 231 (75), 216 (100); Anal. Cald for $C_{18}H_{22}N_6$: C, 67.06; H, 6.88; N, 26.06. Found: C, 67.36; H, 7.15; N, 25.81.

General Procedure for the Optical Purity Determination of Chiral 4-amino-1,2,4-triazoles by fragmentation with LTA. To a solution of the corresponding 4-amino-1,2,4-triazole (1 mmol) in methanol (10 ml) at 0 °C lead tetraacetate (LTA, 1 mmol) in methanol (5 ml) was added. The mixture was stirred at room temperature for 2 h and then evaporated. The residue was treated with CH_2Cl_2 (30 ml) and the suspension filtered on Celite. The solvent was removed and the remaining nitrile(s) was dried *in vacuo*. To a solution of the residue in chloroform (2 ml) under argon (*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPACl, 1.5 molar excess) and triethylamine (2.5 molar excess) were added. The mixture was stirred at room temperature for 1 h and then diethyl ether was added. The precipitate was filtered off and the solvent was evaporated to give the corresponding Mosher's derivative(s). Finally, the diastereomeric excess was determined by ^{1}H-NMR.

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