Synthesis of Functionalized Bicyclic Triazoles from Chiral Aziridines

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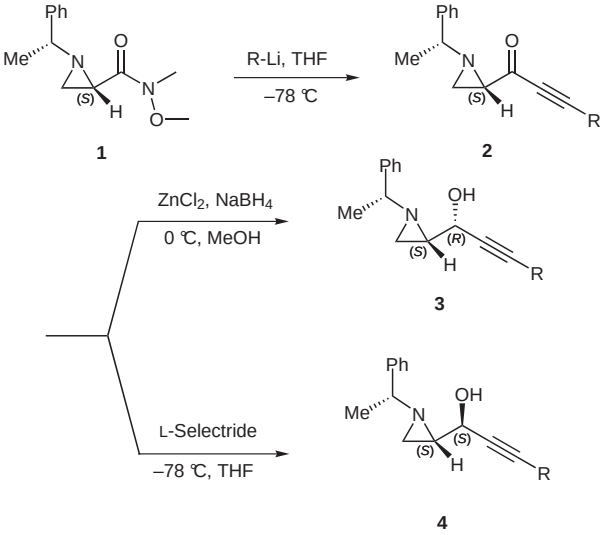
Abstract: Enantiomerically pure 3-substituted-5-amino-4-hydroxy-5,6-dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]triazoles were synthesized efficiently from the sequential reactions including a regioselective ring-opening of 1-aziridine-2-yl-propargylic alcohols by azidotrimethylsilane and the subsequent intramolecular 1,3-dipolar cycloaddition between alkyne and azide.

Key words: aziridine, triazole, cycloaddition, alkyne, azide

The importance of triazoles found in many biologically active products has been emphasized in organic chemistry. They consist of essential structural backbone of various pharmaceuticals with anti-HIV,[1] antimicrobial,[2] β-lactamase inhibitory,[3] antiviral and antiepileptic[4] activities. Therefore, methodologies for the preparations of triazoles have attracted much attention from both academia and industry.[5] However, there are only a few preparative methods available from azidoallenes,[6] hexofuranose,[7] 2-carboxy-4-chlorophenylazide[8] and polystyrene-sulfonyl hydrazide.[9] The requirement for a more efficient preparative method toward enantiomerically pure functionalized bicyclic triazoles prompted us to develop a new facile synthetic route. Herein we report a new strategy for the efficient preparation of multi-functionalized bicyclic triazoles from the sequential reactions including a regioselective ring-opening of 1-aziridin-2-yl-propargylic alcohols by azidotrimethylsilane and the subsequent intramolecular 1,3-dipolar cycloaddition between alkyne and azide.

We recently reported the preparation of the Weinreb amide from the commercially available chiral aziridine-(2*S*)-carboxylic acid menthol ester[10] in one step with Weinreb's amine hydrochloride and $AlMe_3$ in CH_2Cl_2 in high yield.[11] The amide **1** was reacted with various lithium acetylides to provide the corresponding alkynyl ketones **2** in high yields. We also reported the chelation-controlled stereoselective reduction of 2-acylaziridines toward *erythro* isomer in the presence of $ZnCl_2$ and $NaBH_4$ in MeOH in high yields.[11] This methods afforded various (1*S*,2*R*)-1-aziridin-2-yl-propargylic alcohols **3** in good yield.[12] The other *threo* isomers, (1*S*,2*S*)-1-aziridin-2-yl-propargylic alcohols **4** were prepared by the reported reduction method with L-Selectride® in good yield (Scheme 1).[13] Both of 1-aziridin-2-yl-propargylic alcohols **3** and **4** were utilized for the preparation of *cis*- and *trans*-3-substituted-5-amino-4-hydroxy-5,6-dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]triazole.



Scheme 1 Preparation of 1-aziridin-2-yl-propargylic alcohols

Since the aziridine nitrogen is quite basic and also nucleophilic, ring-opening reactions are initiated by the formation of the aziridinium ion intermediate.[10] When 1-aziridine-2-yl-propargylic alcohols were reacted with azidotrimethylsilane an activated aziridinium species **I** would be produced by the silylation of the aziridine nitrogen. Then, regioselective ring-opening reaction with the cleavage of C(3)–N bond proceeded by an azide that was liberated from azidotrimethylsilane.[14] Treatment of ring-opening product with 6 N aqueous HCl solution afforded azido amimo alcohol **II**. This crude reaction mixture was concentrated, dissolved in DMF and heated to 130 °C (Scheme 2).[15]

Consequently, the intramolecular 1,3-dipolar cycloaddition[16] efficiently converted the azido alkynes **II** to the corresponding bicyclic triazoles **5**. We applied the same reaction condition toward various amino hydroxyl substituted bicyclic triazoles starting from 1-aziridine-2-yl-propargylic alcohols **3** bearing phenyl (**5a**), substituted phenyl (**5b–e**), pyridyl (**5f**), pyrenyl (**5g**), linear alkyl (**5h**)

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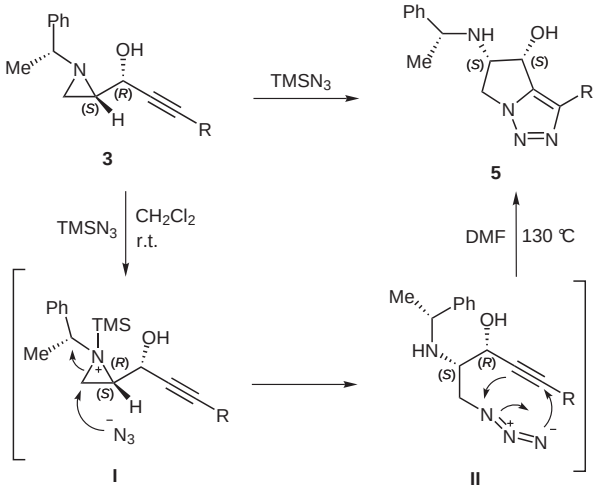


Scheme 2 Preparation of bicyclic triazole and its reaction mechanism

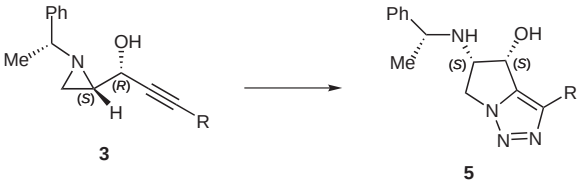
and cyclic alkyl (**5i**) substituents on R in 74–89% yields (Table 1).

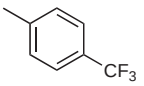
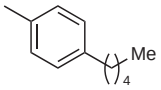
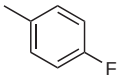
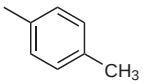
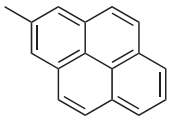
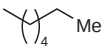
The same reaction could be applicable with the *threo* isomers of (1*S*,2*S*)-1-aziridin-2-yl-propargylic alcohols **4** for the preparation of *trans*-3-substituted-(5*S*)-amino-(4*R*)-hydroxy-5,6-dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]triazoles **6** represented by the examples of **6a** and **6i** in 83% and 89% yield, respectively (Table 2).

The absolute configuration at C-4 of the 3-substituted-4,5-difunctionalized bicyclic triazoles was indirectly established by measuring the coupling constants of the two vicinal protons at C-4 and C-5. The measurement of two sets of the coupling constants (**5a** and **6a**, **5i** and **6i**) clearly established the substitution patterns of *cis*- and *trans*-4,5-difunctionalized bicyclic triazoles (Table 3) by the difference of 1.3 Hz and 2.2 Hz, respectively.

The removal of α-methylbenzyl nitrogen protecting group from bicyclic triazoles (**5** or **6**) was achieved at ease by hydrogenation at room temperature in the presence of $Pd(OH)_2$ as a catalyst. *N*-α-Methylbenzyl-protected amino bicyclic triazoles are also convertible to the corresponding cyclic carbamate **7** at which stage the α-methylbenzyl nitrogen protecting group can also be removed.[17] This procedure was exemplified with the compound **5a**. Hydrogenation of **5a** in the presence of $Pd(OH)_2$ as a catalyst produced free amino alcohol **9a** in 84% yield.[18] The removal of α-methylbenzyl nitrogen protecting group from **5a** also could be achieved by the sequential reactions. At first bicyclic triazole **5a** was converted to the corresponding cyclic carbamate **7a** in 84% yield by treatment of triphosgene and NaH. The subsequent removal of the α-methylbenzyl group was accomplished by treating with anisole and $MeSO_3H$ to give **8a** in 93% yield. Then the cyclic carbamate **8a** was hydrolyzed in aqueous EtOH using LiOH to provide the corresponding free amino bicyclic triazole **9a** in 82% yield (Scheme 3). This procedure was applicable to the compounds bearing hydrogenation-sensitive functional group like olefin on **5i** and **6i**.

Table 1 Synthesis of *cis*-3-Substituted-5-amino-4-hydroxy-5,6-dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]triazole



Products	R	Yield (%)[a,b]
5a		83
5b		85
5c		84
5d		81
5e		86
5f		74
5g		78
5h		75
5i		89

[a] All products characterized by ^1H NMR, IR spectroscopy, and mass spectrometry.
[b] Isolated yields after purification.

In conclusion, we developed a new method for the preparation of enantiomerically pure *cis*- and *trans*-3-substituted-5-amino-4-hydroxy-5,6-dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]triazole from the sequential reactions including a regioselective ring-opening of 1-aziridine-2-yl-propargylic alcohols by azidotrimethylsilane and intramolecular 1,3-dipolar cycloaddition between alkyne and azide.

Acknowledgment

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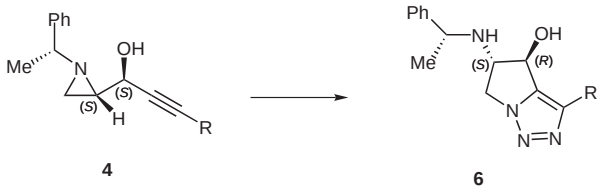
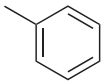
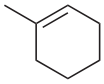
Table 2 Synthesis of *trans*-3-Substituted-5-amino-4-hydroxy-5,6-dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]triazole

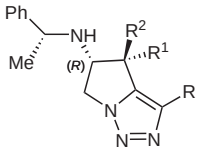


4 **6**

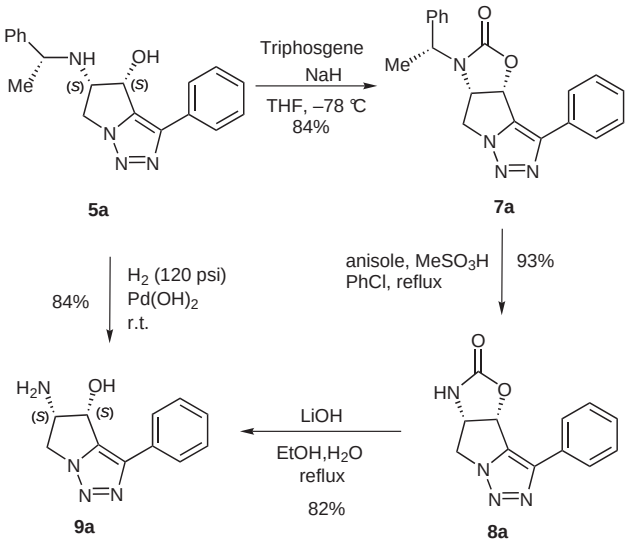
Products	R	Yield (%)
6a		83
6i		89

[a] All products characterized by ^{1}H NMR, IR spectroscopy, and mass spectrometry.
[b] Isolated yields after purification.

Table 3 Coupling Constants of *cis*- and *trans*-3-Substituted-4-hydroxy-5-amino Bicyclic Triazoles



Compd	R	R^1	R^2	$J_{4,5}$ (Hz)
5a	Ph	OH	H	5.6
5i	1-Cyclohexenyl	OH	H	5.5
6a	Ph	H	OH	4.3
6i	1-Cyclohexenyl	H	OH	3.3



5a **7a** **9a** **8a**

Scheme 3 Formation of carbamate and removal of the nitrogen protecting group

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(12) The same product, (1*S*,2*R*)-1-aziridine-2-yl-propargylic alcohol (**3**), could be obtained from addition reactions of the aziridine-(2*S*)-carboxaldehyde with the corresponding organolithium reagents to afford aziridine-(2*S*)-propargylic alcohols. The chelation controlled reduction of the carbonyl group of 2-acylaziridine as shown in Scheme 1 provided better stereoselectivity than the addition of organolithium reagents to the aziridine-(2*S*)-carboxaldehyde. See: Park, C. S.; Choi, H. G.; Lee, H. J.; Lee, W. K.; Ha, H.-J. *Tetrahedron: Asymmetry* **2000**, *11*, 3283.
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(15) **Preparation of (4*S*,5*S*)-4-Hydroxy-3-phenyl-5-{(1*R*)-1-phenylethylamino)-5,6-dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]triazole(5a).**
To a solution of aziridine-(2*S*)-propargyl alcohol (**3a**, 110 mg, 0.40 mmol) in 2.00 mL of CH_2Cl_2 under nitrogen atmosphere was added $TMSN_3$ at r.t. The mixture was stirred for 3 h at r.t. then quenched with 6 N HCl. The aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, and the solvent was evaporated to give product as yellow oil. The crude reaction product was dissolved in 2.10 mL of DMF at r.t. The mixture was stirred under a nitrogen atmosphere for 16 h at 130 °C. The solvent was evaporated to give the crude product as a yellow oil which was purified by silica gel flash chromatography with 50% EtOAc–hexane to give 106 mg of **5a** as a white solid in 83% yield; mp 128–129 °C; $[\alpha]_D^{24}$ = +38.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 7.4 Hz, 2 H), 7.37–7.25 (m, 8 H), 4.78 (d, *J* = 5.6 Hz, 1 H), 4.51 (dd, *J* = 11.6, 6.9 Hz, 1 H), 4.10 (dd, *J* = 11.5, 6.8 Hz, 1 H), 4.01 (q, *J* = 6.4 Hz, 1 H), 3.92 (td, *J* = 6.9, 5.6 Hz, 1 H), 1.46 (d, *J* = 6.4 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.0, 142.3, 138.1, 130.4, 129.1, 128.9, 128.2, 128.0, 126.9, 126.2, 64.5, 62.9, 57.2, 51.1, 24.3. Anal. Calcd for $C_{19}H_{20}N_4O$: C, 71.2; H, 6.29; N, 17.5. Found: C, 71.3; H, 6.30; N, 17.2.

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(18) **Removal of α-Methylbenzyl Nitrogen Protecting Group from 5a**.

To a solution of phenylethylamino bicyclic triazole (**5a**, 110 mg, 0.34 mmol) in 1.90 mL of MeOH was added $Pd(OH)_2$ at r.t. The mixture was stirred for 30 h under 120 psi of H_2 (g)at r.t. then the catalyst was filtered and washed with MeOH. The solvent was evaporated to give product as yellow oil which was purified by recrystallization from CH_2Cl_2 to give 61 mg (84%) of 3-phenyl-5-amino-4-hydroxy-5,6-dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]triazole(**9a**) as a white solid; mp 197–198 °C; $[\alpha]_D^{24}$ = +106.5 (*c* 0.7, CH_3OH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.0 Hz, 2 H), 7.38 (t, *J* = 7.3 Hz, 2 H), 7.28 (t, *J* = 7.5 Hz, 1 H), 5.03 (d, *J* = 5.5 Hz, 1 H), 4.55 (dd, *J* = 11.1, 7.4 Hz, 1 H), 4.14 (td, *J* = 7.4, 5.6 Hz, 1 H), 3.96 (dd, *J* = 11.1, 7.3 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.6, 139.3, 130.6, 128.8, 128.2, 125.9, 65.4, 58.6, 51.7. Anal. Calcd for $C_{11}H_{12}N_4O$: C, 61.1; H, 5.59; N, 25.9. Found: C, 61.2; H, 5.53; N, 26.0.