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Intramolecular Huisgen [3+2] cycloaddition in water: synthesis of fused pyrrolidine–triazoles

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ABSTRACT

The intramolecular alkyne–azide Huisgen [3+2] cycloaddition reaction as a 'click-chemistry' reaction without a metal catalyst has been studied under aerobic conditions. The synthesis of various pyrrolidine–triazole hybrid compounds has also been achieved by using this intramolecular cycloaddition reaction in water with complete 1,5-regioselectivity.

1. Introduction

Subsequent to the isolation of potent glycosidase inhibitors,[1] such as nojirimycin, 1-deoxynojirimycin, swanisonine, casuarine from natural sources, there has been a growing interest in the chemistry, biochemistry, and pharmacology of these compounds, known as 'imino-sugars'.[2] Therefore, an attractive approach to potent inhibitors is toward design molecules with a half-chair conformation, which is known to be the transition state of the enzyme catalyzed reactions.[3] In this context, a new class of hybrid compounds in which a piperidine or pyrrolidine nucleus is fused to a triazole, tetrazole, pyrazole, or a pyrrole ring have been synthesized and studied as inhibitors of various glycosidases.[4] In particular, the synthesis of pyrrolidine-tetrazoles **1**, piperidine–triazoles **2** and **3,** and sugar-derived morpholine triazoles **4** has been accomplished starting from sugars in several steps (Fig. 1).[2,5]

Further attention has recently been focused on 1,2,3-triazole derivatives[6] since they are considered as biologically important molecules with activities such as antibacterial,[7] anti-HIV,[8] herbicidal,[9] antitumor,[10] tuberculosis inhibition,[11] tyrosinase inhibition,[12] antiallergic,[13] and glycosidase inhibition.[4,14] 1,2,3-Triazoles also offer an appealing structural motif in peptidomimetic research because their structural and electronic characteristics are similar to those of a peptide bond.[15] The Huisgen dipolar cycloaddition reaction between organic azides and alkynes is an attractive route to 1,2,3-triazole heterocycles,[16] which have also found a number of important applications in the pharmaceutical and agrochemical industries.[17] Stimulated by its high efficiency, and functional group compatibility, the alkyne–azide cycloaddition has also been widely applied to the construction of organic and bioorganic molecular architectures.[18]

The main problems associated with this traditional method are long reaction times, high temperatures, and the formation of mixtures of 1,4- and 1,5-disubstituted triazoles with poor regioselectivity. Sharpless et al. have developed a high yielding synthesis of 1,2,3-triazoles using a Cu(I)-catalyst with an excellent level of 1,4-regioselectivity under mild conditions using a set of reactions defined as the 'click-chemistry' approach.[19] Recently, regioselective 1,5-disubstituted triazoles have been prepared exclusively from terminal alkynes and alkyl azide catalyzed by $Cp^*RuCl(PPh)_3$ in refluxing benzene.[20] These catalytic reactions solve the problems associated with the traditional method. However, it is also known that alkynes attached to electron-withdrawing groups enhance the rate of the cycloaddition reaction; high levels of regioselectivity have been achieved, when the cycloaddition is carried out between internal/terminal-activated alkynes with different azides under mild conditions.[21] In a continuation of our efforts toward the synthesis of structural scaffolds of biological importance,[22] and the study of intermolecular Huisgen [3+2] cycloadditions for making hybrid triazolo-skeletons in water[23] we were prompted to develop a metal free intramolecular alkyne–azide cycloaddition[24] approach for the synthesis of various triazolo-hybrid compounds with different ring sizes (Scheme 1). Herein we report the synthesis of pyrrolidine–triazole hybrid molecules using an intramolecular Huisgen cycloaddition in water, which subsequently eliminate the use of organic solvents making this process a green one.[25]

2. Results and discussion

The retrosynthetic analysis of our strategy to synthesize pyrrolidine–triazole hybrid molecules is shown in Scheme 2. Compound

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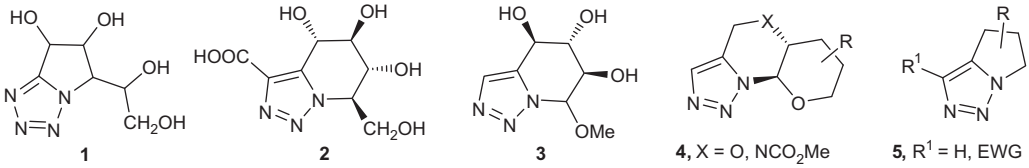
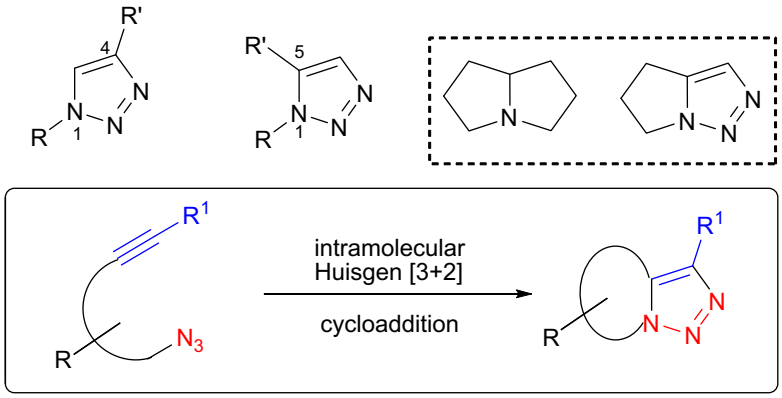
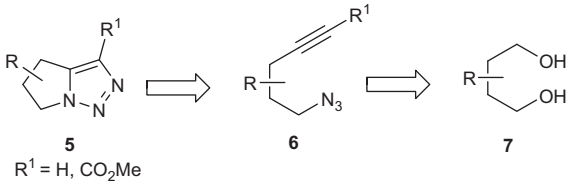


Figure 1.



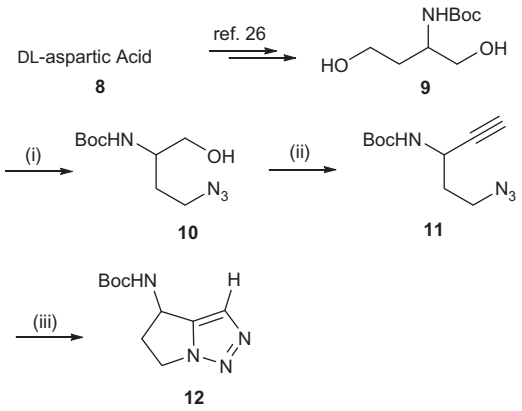
Scheme 1. Complete 1,5-regioselectivity in intramolecular Huisgen [3+2] dipolar-cycloaddition reactions.

6 was visualized as a main synthetic intermediate from which fused pyrrolidine–triazoles could be prepared using an intramolecular Huisgen [3+2] cycloaddition with only 1,5-regioselectivity. Compound **6** could in turn be derived from the protected 1,4-diol **7** through standard synthetic transformations. We initially started with the simple 1,4-diol **9** prepared from commercially available DL-aspartic acid by following the reported procedure.[26] Selective protection of the less hindered alcohol with TsCl followed by nucleophilic substitution with NaN_3 in DMSO/1,4-dioxane gave azido-alcohol compound **10** in 74% yield. Our next aim was to introduce an alkyne moiety in place of the hydroxyl group in compound **10**. For this purpose, we first proceeded with the oxidation of the hydroxyl group of **10** to its corresponding aldehyde using IBX in EtOAc at reflux for 4 h,[27] followed by its conversion into an azido-alkyne compound **11** using Ohira's conditions[28] with 68% yield over two steps. The intramolecular Huisgen cycloaddition of **11** was carried out in water by heating at 70 °C for 1 h to give the corresponding pyrrolidine-triazolo hybrid compound **12** with 71% yield (Schemes 3 and 4).



Scheme 2. Retrosynthetic analysis of pyrrolidine–triazole hybrids via intramolecular Huisgen [3+2] cycloaddition reactions.

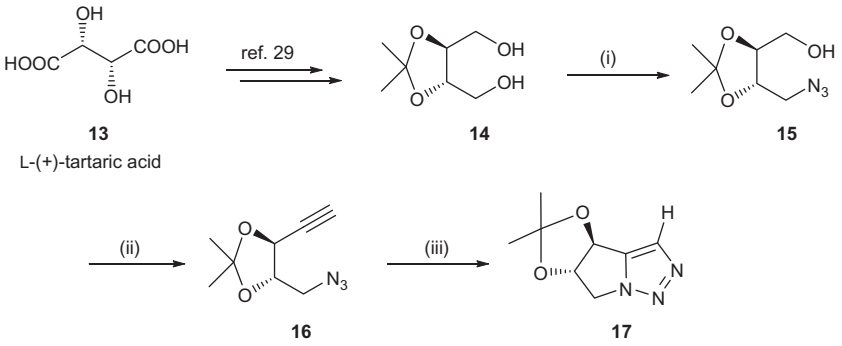
Next, L-(+)-tartaric acid **13** was converted into 1,4-diol **14** according to the reported procedure.[29] Compound **14** was converted into azido-alcohol **15** by using a two step one pot procedure. For this purpose, compound **14** was subjected to mono-protection with NaH/TsCl in dry THF at 0 °C for 2 h followed by nucleophilic substitution with NaN_3 in 1,4-dioxane/DMSO at 65 °C for 6 h to provide azido-alcohol **15** in 87% yield. Azido-alcohol **15** was converted into the corresponding azido-alkyne **16** using the sequence of IBX-oxidation followed by Ohira's conditions with 82% yield. The



Scheme 3. Reagents and conditions: (i) (a) Et_3N (1.5 equiv), TsCl (1.2 equiv), dry DCM, 0 °C, 2 h, (b) NaN_3, DMSO/1,4-dioxane (1:1), 65 °C, 6 h, 74% over two steps; (ii) (a) IBX (3 equiv) EtOAc/Acetone (10:1), 80 °C, 4 h, (b) Ohira's reagent (1.5 equiv), K_2CO_3, MeOH, rt, overnight, 68% over two steps; (iii) H_2O, 70 °C, 1 h, 71%.

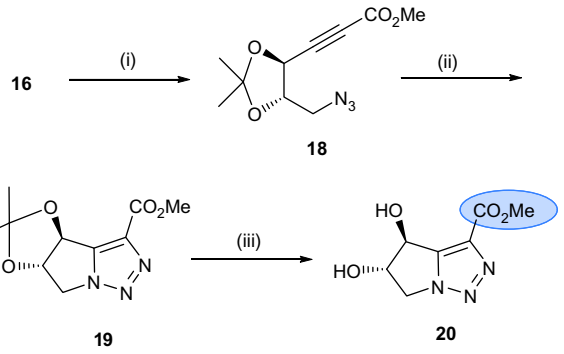
intramolecular Huisgen cycloaddition of **16** was carried out in water by heating at 70 °C for 1 h to give pyrrolidine–triazole compound **17** in 60% yield (Scheme 4). Cycloadduct **17** was found to be unstable when left for a long time, causing lower yields under thermal cycloaddition conditions. Further deprotection of the acetonide moiety from compound **17** under several different conditions also leads to a complex reaction mixture from which the desired product could not be isolated. Here, our efforts were focused on increasing the stability and yield of the cycloadduct by making the alkyne moiety activated through the attachment of an electron withdrawing group at the alkyne terminal position.

The attachment of a carboxylic ester moiety as the electron withdrawing group on the terminal position of the alkyne was carried out by treating compound **16** with sodamide (1.1 equiv) in dry THF at −10 °C followed by trapping with methyl chloroformate (1.2 equiv) to give **18** in 86% yield. The activated alkyne compound **18** quickly underwent [3+2] cycloaddition by heating in water at 70 °C for 30 min, to give the substituted fused pyrrolidine–triazole



Scheme 4. Reagents and conditions: (i) (a) NaH, TsCl, dry THF, 0 °C, 2 h, (b) NaN_3, DMSO/1,4-dioxane (1:1), 65 °C, 6 h, 87% over two steps; (ii) (a) IBX (3 equiv), EtOAc/Acetone (10:1), 80 °C, 4 h, (b) Ohira's reagent (1.2 equiv), K_2CO_3, MeOH, rt, overnight, 82% over two steps; (iii) H_2O, 70 °C, 1 h, 60%.

compound **19** in 91% yield. Cycloadduct **19** was found to be stable when left for a long time under freezing conditions. Next, the acetonide deprotection of **19** was carried out in *p*-TSA/MeOH to give the corresponding dihydroxy pyrrolidine–triazole **20** in 78% isolated yield. Further functionalization can be carried out at the ester moiety on the trizole-ring as shown in Scheme 5. All the new compounds were fully characterized by spectroscopic means.



Scheme 5. Reagents and conditions: (i) $NaNH_2$ (1.2 equiv), dry THF, −10 to 0 °C, $ClCO_2Me$ (1.2 equiv), 2 h, 86%; (ii) H_2O (8 mL), 70 °C, 30 min, 91%; (iii) *p*-TSA (cat.), MeOH, rt, 2 h, 78%.

3. Conclusion

In conclusion, we have demonstrated the intramolecular Huisgen [3+2] dipolar cycloaddition as a 'click-reaction' in water for the synthesis of various pyrrolidine–triazoles. Azido-alkynes derived from amino acid/tartaric acid have been used and an alkyne attached to an electron withdrawing group provides better yield and stability to the product. The present approach can be used as a general strategy for the rapid conversion of any 1,4-diol structural motifs to the corresponding fused pyrrolidine–triazoles.

4. Experimental

4.1. General methods

All reagents were used as supplied. The reactions involving hygroscopic reagents were carried out under an argon atmosphere using oven-dried glassware. THF was distilled from sodium-benzophenone ketyl prior to use. Reactions were followed by TLC using 0.25 mm Merck silica gel plates (60F-254). Optical rotations were measured using a JASCO P-1020 digital polarimeter using Na-light. The NMR spectra were recorded on a Bruker system (200 MHz for ^1H and 75 MHz for ^{13}C). The chemical shifts are reported using the δ (delta) scale for ^1H and ^{13}C spectra. Choices of deuterated solvents ($CDCl_3$, D_2O) are indicated below. LC–MS was recorded using the electrospray ionization technique. All of the organic extracts were dried over sodium sulfate and concentrated under an aspirator vacuum at room temperature. Column chromatography was performed using (100–200 and 230–400 mesh) silica gel obtained from M/s Spectrochem India Ltd. Room temperature is referred as rt.

4.2. *tert*-Butyl(4-azido-1-hydroxybutan-2-yl)carbamate 10

To a stirred solution of compound **9** (1.0 g, 4.87 mmol) and Et_3N (1.0 mL, 7.31 mmol) in dry DCM (10 mL) was added dropwise TsCl (1.11 g, 5.85 mmol) solution in 5 mL dry DCM under an inert atmosphere. The combined mixture was stirred for 4 h at the same temperature and the solvent was evaporated under reduced pressure. The resulting crude material was taken in DMSO/1,4-dioxane (1:1, 10 mL) and heated with NaN_3 (0.633 g, 9.74 mmol) at 65 °C for 6 h. The reaction mixture was quenched with a dilute $NaHCO_3$ solution (10 mL) and extracted with EtOAc (2 × 15 mL); the combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification over silica gel column chromatography gave **10** (0.83 g, 74% in two steps) as a light yellow liquid. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.55–1.87 (m, 11H), 2.91 (m, 2H), 3.69–3.85 (m, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.21 (3C), 31.04, 43.54, 54.01, 63.02, 80.64, 156.13. Anal. Calcd for $C_9H_{18}N_4O_3$ (230.26): C, 46.94; H, 7.88; N, 24.33; Found: C, 46.89; H, 7.84; N, 24.37.

4.3. *tert*-Butyl(5-azidopent-1-yn-3yl)carbamate 11

To a stirred solution of compound **10** (0.6 g, 2.60 mmol) in EtOAc (26 mL) was added *o*-iodoxy-benzoic acid (IBX) (2.18 g, 7.82 mmol) and heated at reflux at 80 °C for 4 h. The reaction was cooled at rt and filtered under suction to remove the solid residue and washed twice with a sat. $NaHCO_3$ solution followed by a brine solution, dried over Na_2SO_4, and concentrated under reduced pressure to give the corresponding aldehyde in almost quantitative yield. The crude aldehyde was taken in MeOH (6 mL) and stirred along with Ohira's reagent (0.75 g, 3.91 mmol) followed by the addition of solid anhydrous K_2CO_3 (1.08 g, 7.82 mmol) at 0 °C for 15 min and at rt for an additional 8 h to complete the reaction. The progress of the reaction was monitored by TLC; when complete, evaporation of the solvent and purification by column chromatography gave **11** (0.40 g, 68% in two steps). ^1H NMR (200 MHz, $CDCl_3$) δ: 1.49–1.83 (m, 11H), 2.37 (d, 1H Alkyne), 2.85 (m, 2H), 4.13 (m 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.19 (3C), 31.23, 43.05, 47.23, 72.09, 80.64, 83.10, 156.19. Anal. Calcd for

$C_{10}H_{16}N_4O_2$ (224.26): C, 53.56; H, 7.19; N, 24.98; Found: C, 53.51; H, 7.14; N, 25.01.

4.4. *tert*-Butyl(5,6-dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]triazol-4-yl)carbamate 12

Compound **11** (0.35 g, 1.56 mmol) was taken in water (6 mL) and heated at 70 °C for 1 h with stirring. The reaction was then cooled down and stirred with EtOAc (10 mL). The organic layer was separated and dried over Na_2SO_4. Evaporation of the solvent and purification of the crude product by column chromatography gave **12** (0.25 g, 71%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.43–1.67 (m, 9H), 2.45–2.61 (m, 2H), 3.49–3.56 (m, 2H), 4.82 (m, 1H), 7.57 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.25 (3C), 37.31, 40.89, 55.68, 80.14, 131.79, 146.56, 156.68. Anal. Calcd for $C_{10}H_{16}N_4O_2$ (224.26): C, 53.56; H, 7.19; N, 24.98; Found: C, 53.49; H, 7.17; N, 24.94.

4.5. ((4*S*,5*S*)-5-(Azidomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol 15

To a stirred solution of compound **14** (1.0 g, 6.17 mmol) in dry THF (15 mL) was added sodium hydride (0.25 g, 6.17 mmol, 60% in mineral oil) at 0 °C for 10 min and then stirred for a further 15 min. Next, a solution of TsCl (1.18 g, 6.17 mmol) in 10 mL dry THF was added dropwise under an inert atmosphere. The combined mixture was stirred for 30 min at the same temperature and then quenched with a dilute $NaHCO_3$ solution. The reaction mixture was extracted with EtOAc (2 × 10 mL) and washed with brine solution; the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to provide a crude *mono*-tosylated slightly yellowish solid compound, which was heated with NaN_3 (1.0 g, 12.35 mmol) in DMSO:1,4-dioxane (10 mL) at 65 °C for 6 h, followed by evaporation of the solvent and the usual work-up and purification by column chromatography to give **15** (1.01 g, 87% in two steps) R_f = 0.70 (8:2 Hexane/EtOAc). $[\alpha]_D^{25} = -69.3$ (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.40 (s, 3H), 1.43 (s, 3H), 2.86 (bs, 1H, OH), 3.31 (dd, *J* = 4.7, 13.2 Hz, 1H), 3.67 (dd, *J* = 3.8, 13.1 Hz, 1H), 3.71–3.85 (m, 2H), 3.90–4.11 (m, 2H), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.67, 26.87, 51.63, 61.62, 76.07, 78.31, 109.70; LC–MS (ESI-TOF): *m*/*z* = [M+ Na]$^+$ 210.17; Anal. Calcd for $C_7H_{13}N_3O_3$ (187.2): C, 44.91; H, 6.99; N, 22.45; Found: C, 44.89; H, 6.86; N, 22.50.

4.6. (4*S*,5*S*)-4-(Azidomethyl)-5-ethynyl-2,2-dimethyl-1,3-dioxolane 16

Similar to the previous two-step procedure using IBX oxidation and Ohira's condition; (82% from **15**) For **16**: R_f = 0.65 (9:1 Hexane/EtOAc). $[\alpha]_D^{25} = -109.6$ (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.45 (s, 3H), 1.49 (s, 3H), 2.54 (d, 1H, alkyne), 3.29 (dd, *J* = 4.4, 13.4 Hz, 1H), 3.61 (dd, *J* = 3.7, 13.4 Hz, 1H), 4.23 (m, 1H), 4.51 (dd, *J* = 2.1, 7.4, 1H), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.94, 26.48, 50.43, 67.03, 75.12, 79.95, 80.39, 111.13; Anal. Calcd for $C_8H_{11}N_3O_2$ (181.19): C, 53.06; H, 6.12; N, 23.19; Found: C, 53.19; H, 6.25; N, 23.24.

4.7. (3b*S*,6a*S*)-5,5-Dimethyl-6a,7-dihydro-3b*H*-[1,3]dioxolo[4′,5′:3,4]pyrrolo[1,2-*c*][1,2,3]triazole 17

Compound **16** (0.36 g, 2 mmol) was taken in 8 mL of water and heated at 70 °C for 1 hr with stirring after which the reaction mixture was cooled down and stirred with EtOAc (15 mL) for approximately 10 min. The organic layer was separated and dried over Na_2SO_4. Evaporation of the solvent and purification by column chromatography gave **17** (0.219 g, 61%). $[\alpha]_D^{25} = -64.5$ (*c* 0.75, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.47 (s, 3H), 1.50 (s, 3H), 3.48 (dd, 1H), 3.74 (dd, 1H),, 4.48 (m, 1H), 5.12 (d, *J* = 11.6, 1H), 7.66 (s, 1H, alkene) ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.34, 26.42, 51.84, 78.12, 81.05, 110.94, 126.21, 145.86; LC–MS (ESI-TOF): *m*/*z* = [M+H]$^+$; 182.06, [M+Na]$^+$; 204.04, Anal. Calcd for $C_8H_{11}N_3O_2$ (181.19): C, 53.06; H, 6.12; N, 23.19; Found: C, 53.09; H, 6.18; N, 23.31.

4.8. Methyl-3-((4*S*,5*S*)-5-(azidomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propiolate 18

To a stirred solution of compound **16** (0.45 g, 2.48 mmol) in dry THF (10 mL) at −10 °C was added sodium amide (0.11 g, 2.98 mmol) and mixture was stirred for an additional 30 min at the same temperature. Methyl chloroformate (0.28 g, 2.98 mmol) in dry THF (2.0 mL) was added slowly to this stirred solution at −10 °C and then allowed to return to room temperature. The reaction was quenched with NH_4Cl solution (6 mL) and stirred with EtOAc (15 mL). The organic layer was separated and dried over Na_2SO_4 and evaporated under reduced pressure. The crude material was purified by column chromatography to give **18** (0.51 g, 86% yield) R_f = 0.45 (9:1 Hexane/EtOAc).

$[\alpha]_D = -98.7$ (*c* 0.75, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.46 (s, 3H), 1.51 (s, 3H), 3.31 (dd, 1H), 3.64 (dd, 1H), 4.02 (s, 3H), 4.42 (m, 1H), 5.25 (d, *J* = 7.4, 1H), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.96, 26.51, 50.49, 55.21, 72.32, 80.21, 82.85, 87.27, 111.51, 162.65; Anal. Calcd for $C_{10}H_{13}N_3O_4$ (239.23): C, 50.21; H, 5.48; N, 17.56; Found: C, 50.29; H, 5.57; N, 17.48.

4.9. (3b*S*,6a*S*)-Methyl 5,5-dimethyl-6a,7-dihydro-3b*H*-[1,3]-dioxolo[4′,5′:3,4]pyrrolo[1,2-*c*][1,2,3]triazole-3-carboxylate 19

Compound **18** (0.50 g, 2.09 mmol) was taken in water (8 mL) and stirred at 70 °C for 30 min after which the reaction was cooled down and stirred with EtOAc (15 mL) for approximately 10 min. The organic layer was separated and dried over Na_2SO_4. Evaporation of the solvent gave **19** (0.45 g, 91% yields). $[\alpha]_D^{25} = -86.5$ (*c* 1, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.45 (s, 3H), 1.52 (s, 3H), 3.73 (dd, 1H), 3.94 (dd, 1H), 4.10 (s, 3H), 4.51 (m, 1H), 5.41 (d, *J* = 11.6, 1H), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.64, 26.94, 54.56, 58.72, 79.24, 83.16, 111.84, 136.26, 151.92, 172.32; Anal. Calcd for $C_{10}H_{13}N_3O_4$ (239.23): C, 50.21; H, 5.48; N, 17.56; Found: C, 50.32; H, 5.52; N, 17.59.

4.10. (4*S*,5*S*)-Methyl 4,5-dihydroxy-5,6-dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]triazole-3-carboxylate 20

Compound **19** (0.36 g, 1.50 mmol) was taken in MeOH (6 mL) and stirred with *p*-TSA (cat.) at rt for 2 h. Once the reaction was seen to be over by TLC, MeOH was evaporated under reduced pressure and passed through a small pad of silica to give **20** (0.23 g, 78% yields). $[\alpha]_D^{25} = -38.5$ (*c* 0.5, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$/D_2O) δ: 3.75 (dd, 1H), 3.88 (dd, 1H), 4.20–4.54 (m, 4H), 5.43 (d, *J* = 11.6, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 53.96, 64.48, 78.12, 81.46, 132.28, 150.76, 171.94; LC–MS (ESI-TOF): *m*/*z* = [M+H]$^+$; 200.76, [M+Na]$^+$; 222.94, Anal. Calcd for $C_7H_9N_3O_4$ (199.16): C, 42.21; H, 4.55; N, 21.10; Found: C, 42.65; H, 5.83; N, 21.76.

Acknowledgments

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