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Synthesis of thietane nucleosides by glycosidation of thietanose derivatives with nucleobases

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Abstract—Thietane nucleosides were synthesized by the glycosidation of glycosyl fluoride with nucleobase.

1. Introduction

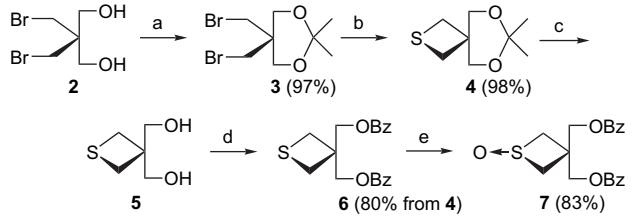
Oxetanocin A (**1**), isolated from *Bacillus megaterium* NK84-0216 in 1986,[1,2] is a nucleoside antibiotic containing an oxetane ring in place of a furanose moiety. Because of its unique structure and broad antiviral spectrum, oxetanocin A and its analogues have been synthesized and evaluated for their biological activities.[3] For example, oxetanocin G, where the adenine base is replaced with a guanine base, exhibits potent antiviral activity against HIV-1 and HSV.[4,5] The carbocyclic analogue of oxetanocin G has been identified as an effective anti-HBV and anti-HSV agent.[6]

More recently, thietane nucleosides, where the oxetane ring is replaced with a thietane ring, have also been synthesized,[7–9] and some of them exhibited antiviral activity against HIV-1.[7] Despite their biological activities, the difficulty involved in synthesizing thietane nucleosides has impeded the investigation of structure–activity relationships and their development as clinical agents. In addition, all the thietane nucleosides reported to date have been synthesized by using Pummerer reaction, and an other method has not been reported so far. Therefore, new methods to synthesize thietane nucleosides are required.

Because of the stronger C–F bond, glycosyl fluoride was not used as a glycosyl donor. However, after the use of glycosyl fluoride as a glycosyl donor with a fluorophilic activator—$SnCl_2$–$AgClO_4$—was introduced by Mukaiyama in 1981,[10] a number of specific fluorophilic reagents have been developed for effective *O*-glycosidation reactions. Glycosyl fluoride is now used as a versatile sugar donor in the synthesis of natural products and carbohydrates because of its enhanced stability and ease of handling as compared to other glycosyl halides.[11] We hypothesized that by preparing glycosyl fluoride even in the case of thietanose, it might be possible to use it as a stable glycosyl donor. In this study, we selected a known thietane nucleoside and its analogue, which are easily prepared as target compounds, and examined their synthesis by the glycosidation of thietanose derivatives with nucleobases.

2. Results and discussion

Precursors **6** and **7** for glycosyl fluoride were prepared from 2,2-bis(bromomethyl)-1,3-propanediol (**2**), as shown in Scheme 1. Thus, 2,2-bis(bromomethyl)-1,3-propanediol (**2**) was converted to isopropylidene-protected derivative **3** with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid with a yield of 97%; this was followed by treatment with sodium sulfide in DMF at 100 °C to give thietane **4** with a yield of 98%. The protecting group in **4** was converted to a benzoyl group to give **6**, which was oxidized using $NaIO_4$ in methanol to give sulfoxide **7** with a yield of 83%.



Scheme 1. Reagents and conditions: (a) 2,2-dimethoxypropane, *p*-TsOH, acetone; (b) $Na_2S{\cdot}9H_2O$, DMF, 100 °C; (c) *p*-TsOH, MeOH; (d) BzCl, DMAP, Et_3N, CH_2Cl_2; (e) $NaIO_4$, MeOH.

Since diethylaminosulfur trifluoride (DAST) was found to be an excellent reagent for the replacement of free hydroxyl groups with fluorine, it is widely used as the most convenient reagent.[12] DAST also converts sulfoxides and sulfides to

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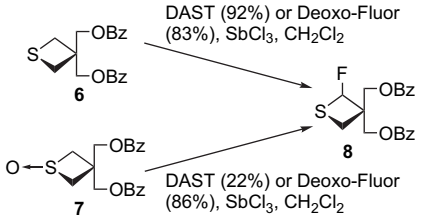
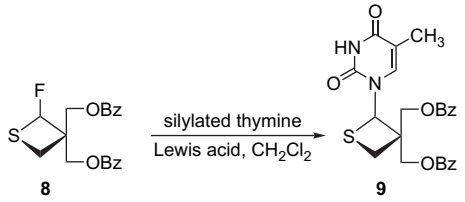
α-fluoro thioethers.[13,14] Recently, bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor) was disclosed as a new broad spectrum fluorinating agent with enhanced thermal stability by Lal and co-workers.[15] Therefore, we investigated the preparation of glycosyl fluoride using DAST and Deoxo-Fluor as fluorinating reagents.

First, we attempted the fluorination of sulfide **6**. Treatments of **6** with DAST and Deoxo-Fluor in dichloromethane produced glycosyl fluoride **8** with yields of 92 and 83%, respectively (Scheme 2). Sulfoxide **7** as well as sulfide **6** reacted with Deoxo-Fluor to produce glycosyl fluoride **8** with a yield of 86%. As described above, we were able to prepare glycosyl fluoride even in the case of thietane derivatives, and **8** was also stable after being purified by silica gel column chromatography.



Scheme 2.

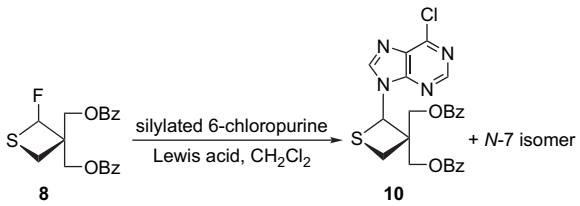
Next, we attempted the glycosidation of **8** with nucleobases. The treatment of glycosyl fluoride **8** with silylated thymine in the presence of TMSOTf–AgOTf as an activating reagent produced thietane nucleoside **9** with a yield of 22% (Scheme 3). The best results were obtained when $AgClO_4$–$SnCl_2$ was used instead of TMSOTf–AgOTf to afford **9** with a yield of 56%.



Lewis acid	Yield (%)
TMSOTf, AgOTf	22
$SnCl_2$, $AgClO_4$	56

Scheme 3.

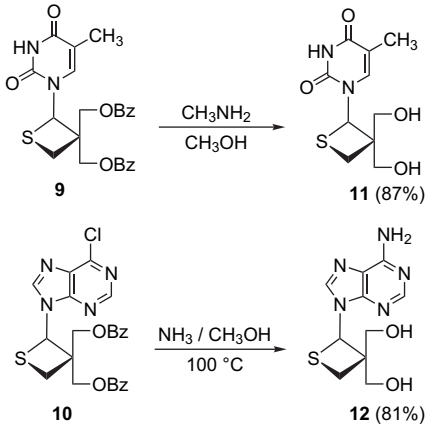
Subsequently, the glycosidation of **8** with silylated 6-chloropurine was examined. As in the case of silylated thymine, glycosyl fluoride **8** reacted with silylated 6-chloropurine in the presence of $AgClO_4$–$SnCl_2$ to produce **10** with a yield of 27% along with the *N*-7 isomer of **10** with a yield of 15% (Scheme 4). It is well known that because of a strain in the oxetane ring, oxetanocin derivatives are treated with a Lewis acid to give its furanosyl derivatives by a ring expansion.[16] Although a thietane ring also has a ring strain, a glycosyl bond of thietanose is more stable than a glycosyl bond of oxetanose. Consequently, thietane nucleosides were obtained with a moderate yield by the glycosylation reaction of glycosyl fluoride with nucleobases in the presence of the Lewis acid.



Lewis acid	Yield (%) **10** (*N*-7 isomer)
BF_3-Et_2O	16 (10)
$SnCl_2$, $AgClO_4$	27 (15)

Scheme 4.

Finally, a free nucleoside **11** was obtained in 87% yield by the deprotection of **9**. A purine nucleoside **12** was also obtained in 81% yield by the treatment of **10** with methanolic ammonia at 100 °C (Scheme 5).



Scheme 5.

3. Conclusion

In summary, the synthesis of thietane nucleoside has been achieved by the glycosylation reaction of glycosyl fluoride with nucleobases. This study reports for the first time the successful synthesis of thietane nucleoside by glycosylation reaction. Thus, it is evident that thietane nucleosides can be synthesized by the condensation of thietanose derivatives with a nucleobase.

4. Experimental section

4.1. General

All melting points were determined on the Yamato melting point apparatus (model MP-2) and were uncorrected. The NMR spectra were recorded on JEOL JNM-LA-300 and JEOL JNM-ECA-500 spectrometers. The chemical shifts are reported in parts per million (δ) relative to TMS (0.0 ppm) as the internal standard, and the signals were expressed as s (singlet), d (doublet), t (triplet), m (multiplet), or br (broad). The values of the coupling constant *J* were provided in hertz. The MS spectra were obtained on JEOL JMS-HX110 and JEOL JMS-700TZ. TLC was performed on Merck

Silica gel 60 F_{254} plates. Column chromatography was conducted using silica gel (Merck, Silica gel 60, 70–230 mesh).

4.1.1. 2,2-Bis(bromomethyl)-1,3-*O*-isopropylidene-1,3-propanediol (3). To a solution of 2,2-bis(bromomethyl)-1,3-propanediol (15.0 g, 57 mmol) in acetone (200 mL), we added 2,2-dimethoxypropane (50 mL) and *p*-toluenesulfonic acid monohydrate (100 mg, 0.5 mmol) at room temperature; this mixture was stirred for 2 h at room temperature. The reaction mixture was neutralized using saturated sodium bicarbonate and the solvent was then evaporated under reduced pressure. The residue was partitioned between ether and water. The separated organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified on a silica gel column, eluted with hexane–ethyl acetate (6:1), to give **3** (16.6 g, 97%) as a colorless solid. Mp 59–60 °C (hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.80 (s, 4H), 3.58 (s, 4H), 1.42 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 99.2, 65.1, 38.0, 36.1, 23.7. EI-LRMS *m*/*z* 285 (M^+-CH_3), 287 (M^+-CH_3+2), 289 (M^+-CH_3+4). Anal. Calcd for $C_8H_{14}Br_2O_2$: C, 31.82; H, 4.67; Br, 52.92. Found: C, 31.87; H, 4.68; Br, 52.78.

4.1.2. 3′,3′-*O*-Isopropylidene-3,3-bis(hydroxymethyl)thiacyclobutane (4). A solution of **3** (17.0 g, 55 mmol) and $Na_2S\cdot 9H_2O$ (15.0 g, 62 mmol) in DMF (200 mL) was stirred at 100 °C for 10 h. The reaction mixture was diluted with ether and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified on a silica gel column, eluted with hexane–ethyl acetate (7:1), to give **4** (9.4 g, 98%) as a yellow solid. Mp 51–52 °C (hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.88 (s, 4H), 2.97 (s, 4H), 1.39 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 98.1, 68.6, 41.3, 31.0, 23.8. EI-LRMS *m*/*z* 174 (M^+). EI-HRMS *m*/*z* 174.0720 (calcd for $C_8H_{14}O_2S$: 174.0714). Anal. Calcd for $C_8H_{14}O_2S\cdot 0.1H_2O$: C, 54.58; H, 8.13. Found: C, 54.43; H, 7.93.

4.1.3. 3,3-Bis[(benzoyloxy)methyl]thietane (6). A solution of **4** (1.0 g, 5.7 mmol) and *p*-toluenesulfonic acid monohydrate (200 mg, 1 mmol) in methanol (50 mL) was stirred at room temperature for 1 h. The reaction mixture was neutralized using saturated sodium bicarbonate and the solvent was then evaporated under reduced pressure. The residue was partitioned between ether and water. The separated organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was dissolved in dry CH_2Cl_2, and triethylamine (2.1 mL, 15.0 mmol), benzoyl chloride (1.6 mL, 13.7 mmol), and DMAP (10 mg) were added to the mixture at 0 °C. After the resulting mixture was stirred at 0 °C for 3 h, the reaction was quenched by adding ice. The reaction mixture was partitioned between ethyl acetate and water. The separated organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified on a silica gel column, eluted with hexane–ethyl acetate (7:1), to give **6** (1.6 g, 80%) as a yellow solid. Mp 79–82 °C (hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.24–7.35 (m, 10H), 4.58 (s, 4H), 3.21 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.3, 133.3, 129.6, 128.5, 66.8, 46.3, 28.8. EI-LRMS *m*/*z* 342 (M^+). EI-HRMS *m*/*z* 342.0952 (calcd for $C_{19}H_{18}O_4S$: 342.0926). Anal. Calcd for $C_{19}H_{18}O_4S$: C, 66.30; H, 5.33; S, 9.36. Found: C, 66.38; H, 5.36; S, 9.63.

4.1.4. 3,3-Bis[(benzoyloxy)methyl]thietan-1-oxide (7). To a solution of **6** (2.8 g, 8.2 mmol) in methanol (200 mL), we added $NaIO_4$ (2.1 g, 9.9 mmol) at 0 °C; this mixture was stirred at room temperature for 21 h. A white solid was formed in the mixture; it was removed by filtration. Next, the mixture was concentrated under reduced pressure. The residue was purified on a silica gel column, eluted with hexane–ethyl acetate (1:2), to give **7** (2.4 g, 83%) as a white solid. Mp 115–116 °C (hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.09–7.46 (m, 10H), 4.46 (s, 2H), 4.42 (s, 2H), 3.79 (d, 2H, *J*=13.1 Hz), 3.44 (d, 2H, *J*=13.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.0, 132.7, 132.6, 128.8, 128.1, 127.9, 127.7, 66.4, 65.7, 55.1, 35.6. EI-LRMS *m*/*z* 358 (M^+). EI-HRMS *m*/*z* 358.0887 (calcd for $C_{19}H_{18}O_5S$: 358.0875). Anal. Calcd for $C_{19}H_{18}O_5S$: C, 63.67; H, 5.06; S, 8.95. Found: C, 63.56; H, 5.06; S, 8.73.

4.1.5. 3,3-Bis[(benzoyloxy)methyl]-2-fluorothietane (8). [Fluorination of sulfide **6**] To a solution of **6** (100 mg, 0.29 mmol) in dry CH_2Cl_2, we added DAST (77 μL, 0.58 mmol) and $SbCl_3$ (1 mg) at room temperature under a nitrogen atmosphere; this mixture was stirred at room temperature for 20 h. The reaction mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate, water, and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified on a silica gel column, eluted with hexane–ethyl acetate (6:1), to give **8** (101 mg, 92%) as an yellow oil.

When Deoxo-Fluor (74 μL, 0.4 mmol) was used instead of DAST, 87 mg of **8** was obtained (83%).

[Fluorination of sulfoxide **7**] To a solution of **7** (1.1 g, 3.1 mmol) in dry CH_2Cl_2, we added Deoxo-Fluor (1.13 mL, 6.12 mmol) and $SbCl_3$ (10 mg) at room temperature under a nitrogen atmosphere; this mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate, water, and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified on a silica gel column, eluted with hexane–ethyl acetate (6:1), to give **8** (949 mg, 86%) as an yellow oil.

When DAST (824 μL, 6.2 mmol) was used instead of Deoxo-Fluor, 242 mg of **8** was obtained (22%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00–8.07 (m, 4H), 7.62–7.54 (m, 2H), 7.48–7.41 (m, 4H), 6.07 (d, 1H, *J*=63.1 Hz), 4.81 (d, 1H, *J*=11.7 Hz), 4.71 (d, 1H, *J*=11.7 Hz), 4.61 (s, 2H), 3.27 (d, 1H, *J*=9.1 Hz), 2.98 (d, 1H, *J*=9.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.2, 166.0, 133.5, 133.3, 129.7, 129.6, 129.5, 129.2, 128.6, 128.5, 94.8 (d, *J*=245.5 Hz) , 65.0, 62.9 (d, *J*=11.7 Hz), 52.9 (d, *J*=21.0 Hz), 25.5. EI-LRMS *m*/*z* 360 (M^+). EI-HRMS *m*/*z* 360.0815 (calcd for $C_{19}H_{17}O_4FS$: 360.0831).

4.1.6. 1-[3,3-Bis(benzoyloxymethyl)thietan-2-yl]thymine (9). A mixture of thymine (87 mg, 0.68 mmol) and HMDS (4 mL) was refluxed for 3 h until the solution became clear. After evaporation, the residue was dissolved in dry CH_2Cl_2 (3 mL). A solution of **8** (122 mg, 0.34 mmol) in dry CH_2Cl_2 (2 mL), $AgClO_4$ (71 mg, 0.34 mmol), and $SnCl_4$ (65 mg, 0.34 mmol) was added to the mixture at 0 °C, and

the mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate, water, and brine. The organic layer was dried over Na_2SO_4, and concentrated in vacuo. The residue was purified on a silica gel column, eluted with hexane–ethyl acetate (1:1), to give **9** (88 mg, 56%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.12 (s, 1H), 8.11–7.95 (m, 5H), 7.62–7.56 (m, 2H), 7.49–7.42 (m, 4H), 6.27 (s, 1H), 4.83 (d, 1H, J=11.6 Hz), 4.63 (d, 1H, J=11.6 Hz), 4.57 (d, 1H, J=12.2 Hz), 4.42 (d, 1H, J=12.2 Hz), 3.25 (d, 1H, J=9.6 Hz), 3.01 (d, 1H, J=9.6 Hz), 1.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.1, 164.8, 161.9, 149.7, 135.8, 132.7, 132.4, 128.8, 128.5, 128.4, 128.8, 127.6, 127.5, 109.6, 65.4, 62.0, 55.6, 52.5, 24.0, 11.4. EI-LRMS m/z 466 (M^+). EI-HRMS m/z 466.1189 (calcd for $C_{24}H_{22}N_2O_6S$: 466.1199).

4.1.7. 9-[3,3-Bis(benzoyloxymethyl)thietan-2-yl]-6-chloropurine (10). A mixture of 6-chloropurine (50 mg, 0.32 mmol) and HMDS (4 mL) was refluxed for 3 h until the solution became clear. After evaporation, the residue was dissolved in dry CH_2Cl_2 (2 mL). A solution of **8** (96 mg, 0.27 mmol) in dry CH_2Cl_2 (1 mL), $AgClO_4$ (56 mg, 0.27 mmol), and $SnCl_4$ (51 mg, 0.27 mmol) was added to the mixture at 0 °C, and the mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate, water, and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified on a silica gel column, eluted with hexane–ethyl acetate (2:1), to give **10** (36 mg, 27%) as a colorless oil and the *N*-7 isomer (20 mg, 15%) of **10** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.66 (s, 1H), 8.38 (s, 1H), 7.96–7.95 (m, 2H), 7.48–7.11 (m, 8H), 6.32 (s, 1H), 4.64 (s, 2H), 4.50 (d, 1H, J=12.0 Hz), 4.21 (d, 1H, J=12.0 Hz), 3.24 (d, 1H, J=10.0 Hz), 2.95 (d, 1H, J=10.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.1, 165.1, 152.1, 151.9, 151.2, 144.3, 133.6, 1332.2, 129.8, 129.2, 128.9, 128.6, 128.4, 128.0, 66.1, 62.9, 53.5, 53.4, 25.0. EI-LRMS m/z 494 (M^+). EI-HRMS m/z 494.0805 (calcd for $C_{24}H_{19}N_4O_4ClS$: 494.0816).

Data for the *N*-7 isomer of **10**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.26 (s, 1H), 8.60 (s, 1H), 8.13–8.10 (m, 2H), 7.66–7.24 (m, 8H), 6.87 (s, 1H), 4.93 (d, 1H, J=11.9 Hz), 4.68–4.66 (m, 2H), 4.29 (d, 1H, J=12.5 Hz), 3.42 (d, 1H, J=9.6 Hz), 3.02 (d, 1H, J=9.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.0, 164.9, 162.4, 152.5, 148.7, 142.4, 133.8, 133.5, 129.7, 129.0, 128.9, 128.7, 128.4, 127.7, 122.8, 65.3, 62.6, 55.5, 53.7, 24.5. EI-LRMS m/z 494 (M^+). EI-HRMS m/z 494.0835 (calcd for $C_{24}H_{19}N_4O_4ClS$: 494.0816).

4.1.8. 1-[3,3-Bis(hydroxymethyl)thietan-2-yl]thymine (11). A methylamine (40% in methanol, 50 mL) was added to **9** (572 mg, 1.2 mmol), and the resulting mixture was stirred at room temperature for 2 h. The mixture was concentrated in vacuo, and the residue was purified on a silica gel column, eluted with 10% methanol in chloroform, to give **11** (269 mg, 87%) as a colorless solid. Mp 204–209 °C (methanol). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.50 (br s, 1H), 8.18 (s, 1H), 5.85 (s, 1H), 4.98 (dd, 1H, J=5.4 and 5.7 Hz), 4.64 (dd, 1H, J=4.5 and 4.6 Hz), 3.59 (dd, 1H, J=5.7 and 10.8 Hz), 3.48–3.32 (m, 3H), 2.87 (d, 1H, J=8.9 Hz), 2.79 (d, 1H, J=8.9 Hz), 1.85 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 164.4, 151.6, 138.7, 108.5, 64.1, 60.5, 56.4, 56.3, 24.7, 12.9. EI-LRMS m/z 258 (M^+). EI-HRMS m/z 258.0685 (calcd for $C_{10}H_{14}N_2O_4S$: 258.0674). Anal. Calcd for $C_{10}H_{14}N_2O_4S$: C, 46.50; H, 5.46; N, 10.85; S, 12.41. Found: C, 46.40; H, 5.44; N, 10.77; S, 12.42.

4.1.9. 9-[3,3-Bis(hydroxymethyl)thietan-2-yl]adenine (12). A solution of **10** (122 mg, 0.25 mmol) in methanolic ammonia (saturated at 0 °C, 10 mL) was heated for 16 h at 100 °C in a steel container. The solvent was removed in vacuo, and the residue was purified on a silica gel column, eluted with 15% methanol in chloroform, to give **12** (54 mg, 81%) as a colorless solid. Mp 246–247 °C (methanol). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.53 (s, 1H), 8.11 (s, 1H), 7.26 (br s, 2H), 6.00 (s, 1H), 5.15 (t, 1H, J=5.5 Hz), 4.50 (t, 1H, J=4.8 Hz), 3.62 (dd, 1H, J=5.5 and 11.1 Hz), 3.55 (dd, 1H, J=5.5 and 11.1 Hz), 3.39 (dd, 1H, J=4.8 and 11.1 Hz), 3.28 (dd, 1H, J=4.8 and 11.1 Hz), 3.00 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 156.0, 152.5, 150.0, 140.7, 118.8, 63.4, 60.2, 55.9, 52.9, 24.3. FAB-LRMS m/z 268 (MH^+). FAB-HRMS m/z 268.0876 (calcd for $C_{10}H_{14}N_5O_2S$: 268.3155). Anal. Calcd for $C_{10}H_{13}N_5O_2S$: C, 44.93; H, 4.90; N, 26.20; S, 12.00. Found: C, 44.93; H, 4.86; N, 26.20; S, 11.76.

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