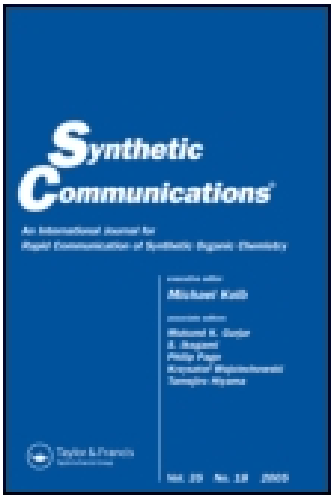

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SYNTHESIS OF 3-AMINO-2,2-DIMETHYL-8-THIA-1-AZASPIRO[4.5]DECANE

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The synthesis of 3-amino-2,2-dimethyl-8-thia-1-azaspiro[4.5]decane is described. Key steps include the addition of prenyl magnesium bromide to a 4-methoxybenzylimine without reversal of stereochemistry and the iodine-initiated aminocyclization to form the azaspirocycle.

Keywords: Grignard reactions; heterocycle; iodoaminocyclization; prenylation; spiro compound

INTRODUCTION

The 1-azaspirocycle is an important structural motif in many alkaloid natural products.[1] For example, cephalotaxine contains a 1-azaspiro[4.4]nonane skeleton,[2] cocculolidine contains a 1-azaspiro[4.5]decane skeleton,[3] and fasicularin contains a 1-azaspiro[5.5]undecane skeleton.[4] The major challenges for the construction of such skeletons come from the formation of the tetra-substituted tertiary carbon center bearing the nitrogen atom that will become the spirocyclic center in the final product and the formation of the two rings of the system. To meet these challenges, several synthetic approaches have been developed, which include the construction of the tertiary nitrogen-bearing carbon center followed by closing the heterocycle,[5] the construction of the tertiary nitrogen-bearing carbon center followed by closing the carbocycle,[6] and the construction of the tertiary nitrogen-bearing carbon center and formation of the spirocycle in a single step.[7] Among the 1-azaspirocycles, some contain other heteroatoms such as sulfur in the ring system and have biological activities. For example, several compounds that contain an 8-thia-1-azaspiro[4.5] decane skeleton have been found to be effective inhibitors of undecaprenyl pyrophosphate synthase,[8] and several others have been used as pesticides.[9] Many of these compounds can potentially be prepared in a way similar to those that do not contain heteroatoms other than nitrogen in the spirocyclic system.

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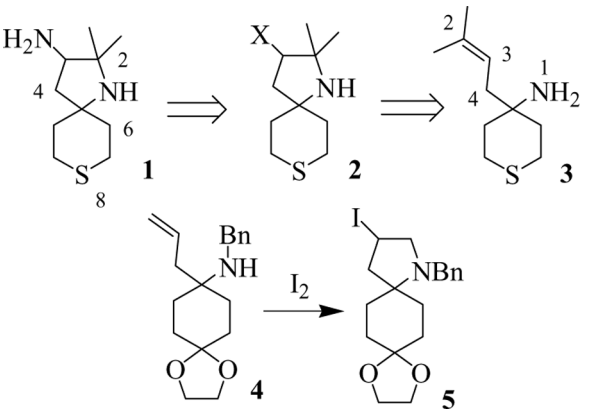
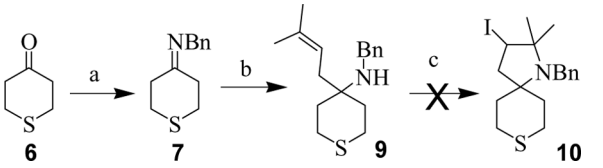
RESULTS AND DISCUSSION

Recently, we have been interested in the preparation of the azaspirocycle 3-amino-2,2-dimethyl-8-thia-1-azaspiro[4.5]decane (**1**). Besides the two common challenges for the preparation of this class of compounds, the hindered tetra-substituted carbon-2 was expected to cause additional difficulties for the synthesis. This tetra-substituted carbon along with the tertiary spirocyclic center makes the secondary amine at position-1 highly hindered. On the other hand, we envisioned that the two methyl groups at carbon-2 may facilitate the synthesis if the spirocyclic system is formed through the formation of the bond between nitrogen-1 and carbon-2 using a cationic approach, that is, using nitrogen-1 to attack a tertiary cation on carbon-2 (Scheme 1). One method for the formation of a cation on carbon-2 is halogenation of the double bond between carbon-2 and carbon-3 of the enamine **3**. Using this approach, the halogen atom on carbon-3 in the spirocyclization product **2** is well suited for conversion to the primary amino group at carbon-3 in **1**. Gratifyingly, a literature search revealed that Diaba et al. used such an iodoaminocyclization method for converting compound **4** to **5** (Scheme 1).[10] With this information in mind, the remaining potential challenges are stereoselective formation of **3** and the conversion of the secondary iodo function of **2** to the amino function of **1**, which are adjacent to a tetra-substituted carbon.

The synthesis was initiated with the preparation of imine **7** from tetrahydro-4H-thiopyran-4-one (**6**)[11] and benzyl amine. Compound **7** could be identified using gas chromatography–mass spectrometry (GC-MS) and purified by distillation under vacuum, but it could not be purified by column chromatography. Analysis by NMR using $CDCl_3$ as solvent also failed because of hydrolysis. After vacuum distillation, **7** was treated with excess prenyl magnesium bromide (**8**)[12] to give the spirocyclization precursor **9**, which was fully characterized (Scheme 2). It is remarkable that addition of **8** to imine **7** proceeded with complete stereocontrol; no product arising from the addition of a reversed prenyl group to **7** was observed.[13] Unfortunately, all attempts to convert **9** to the 1-azaspirocycle **10** under various idodoaminocyclization conditions (**9**/I_2/5% $NaHCO_3$/CH_2Cl_2/rt; **9**/NIS/K_2CO_3/CH_2Cl_2/rt) failed. Because



Scheme 1. Synthesis plan.

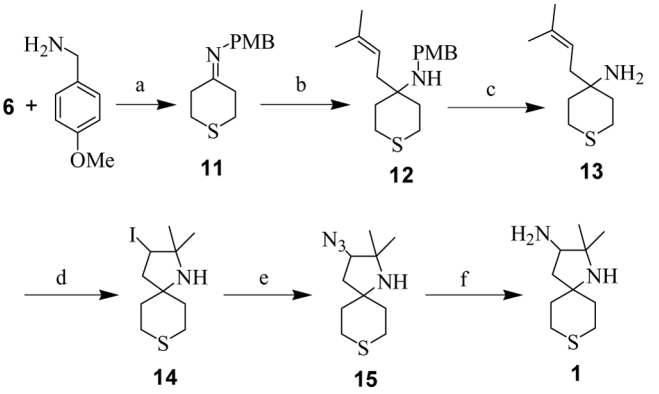


Scheme 2. Reagents and conditions: (a) $BnNH_2$, PhH, reflux; (b) prenyl magnesium, Grignard (**8**), Et_2O, rt, 71% from **6**; and (c) I_2, $NaHCO_3$, CH_2Cl_2, 0%.

Diaba et al. could convert **4** to **5** smoothly in excellent yield,[10] we believe that our failure to form **10** may be attributed to the high steric hindrance around the nitrogen atom in the product.[10,14] Accordingly, to facilitate the spirocyclization, we turned to making the protecting-group-free amine **13**, which would be easier to cyclize because of the reduced steric demand for the carbon–nitrogen bond-formation reaction.

To synthesize **13**, the 4-methoxybenzylimine **11** was prepared from ketone **6** and 4-methoxybenzylamine (Scheme 3). After purification by vacuum distillation, **11** was treated with excess **8**, and the desired product **12** was obtained in 60% yield; no reversed prenylation product was detected.[13] The 4-methoxybenzyl group in **12** was next removed by treatment with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to give the spirocyclization precursor **13** in 70% yield.[15] Iodoaminospirocyclization of **13** was performed at room temperature using I_2 in CH_2Cl_2 under weakly basic conditions[10]; the desired 1-azaspirocycle **14** was obtained in 50% yield. To install the amino group at carbon-3, the iodo function was replaced with an azido group to give **15**,[16] which was reduced under hydrogenation conditions to give the target 1-azaspirocycle **1** in quantitative yield.[17] Despite the steric hindrance from the adjacent tetra-substituted carbon-2, these functional group conversion reactions proceeded smoothly with excellent yields.

In conclusion, we have successfully synthesized 3-amino-2,2-dimethyl-8-thia-1-azaspiro[4.5]decane (**1**) in six steps with a total yield of 15% starting from the commercially available tetrahydro-4H-thiopyran-4-one (**6**). It is remarkable that



Scheme 3. Reagents and conditions: (a) PhH, reflux; (b) **8**, Et_2O, rt, 60% from **6**; (c) DDQ, CH_2Cl_2, H_2O, rt, 15 h, 70%; (d) I_2, $NaHCO_3$ (aq), CH_2Cl_2, rt, 12 h, 50%; (e) NaN_3, MeOH, H_2O, reflux, 12 h, 77%; and (f) 10% Pd/carbon, H_2 (1 atm), EtOH, rt, 24 h, 95%.

azaspirocycle **10** was not accessible from **9** using an iodoaminocyclization approach. This was probably due to the high steric hindrance of **9**, while the less sterically hindered **13** could be cyclized to give **14** in good yield. Prenylation of benzylimines such as **7** and **11** gave products with retention of stereochemistry of the prenyl group.

EXPERIMENTAL

N-[Tetrahydro-4-prenyl-2H-thiopyran-4-yl]-*N*-benzylamine (9)

Tetrahydro-4H-thiopyran-4-one (**6**, 4.64 g, 40 mmol; commercially available but prepared according to the reported procedure[11]) and benzylamine (4.4 mL, 40 mmol) were dissolved in benzene (100 mL), and the solution was heated to reflux for 5 h with azeotropic removal of water using a Dean–Stark apparatus. After cooling to rt, the solvent was removed under reduced pressure, and the residue was distilled under vacuum, giving imine **7** as a colorless liquid (7.8 g, 95%). Analysis by NMR using $CDCl_3$ as solvent failed because of hydrolysis, but GC-MS showed that the product was pure and had the correct molecular weight. Prenyl magnesium bromide (**8**), which was prepared from prenyl bromide (1.7 mL, 15 mmol) and magnesium turnings (1.8 g, 75 mmol) in dry Et_2O (40 mL) at rt according to a reported procedure, was added dropwise to the solution of imine **7** (1.4 g, 7.0 mmol) in dry Et_2O (20 mL).[12] The mixture was stirred at rt overnight, poured into saturated NH_4Cl, and extracted with Et_2O. The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash-column chromatography (SiO_2, hexanes–EtOAc, 5:1) gave **9** as a light yellow thick oil (1.4 g, 71%): $R_f = 0.4$ (SiO_2, hexanes–EtOAc, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, $J = 6.8$ Hz, 2H), 7.31 (t, $J = 7.2$ Hz, 2H), 7.24 (t, $J = 7.2$ Hz, 1H), 5.15 (tt, $J = 7.2$, 1.2 Hz, 1H), 3.59 (s, 2H), 3.09 (dt, $J = 13.6$, 11.2 Hz, 2H), 2.33 (dt, $J = 13.2$, 4.4 Hz, 2H), 2.15 (d, $J = 7.6$ Hz, 2H), 1.92 (dt, $J = 14.4$, 3.2 Hz, 2H), 1.72 (s, 3H), 1.68 (dt, $J = 14.4$, 2.4 Hz, 2H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.30, 134.59, 128.34, 128.21, 126.85, 118.55, 53.43, 45.12, 37.52, 36.52, 26.18, 23.56, 18.17. HRMS-ESI m/z $[M + H]^+$ calcd. for $C_{17}H_{26}NS$: 276.1786; found 276.1793.

N-[Tetrahydro-4-prenyl-2H-thiopyran-4-yl]-*N*-(4-methoxy-benzyl)amine (12)

Imine **11** was prepared from **6** (4.64 g, 40 mmol) and 4-methyoxybenzylamine (5.2 mL, 40 mmol) as a colorless liquid (8.9 g, 95%) after distillation under vacuum using the procedure for the preparation of **7**. Like **7**, analysis of **11** by NMR using $CDCl_3$ as solvent failed because of hydrolysis. Prenyl magnesium bromide (**8**), which was prepared from prenyl bromide (9.24 mL, 80 mmol) and magnesium turnings (9.6 g, 400 mmol),[12] was added dropwise to the solution of **11** (8.9 g, 38 mmol) in dry Et_2O (70 mL). After stirring at rt overnight, the mixture was poured into saturated NH_4Cl, and the product was extracted into Et_2O. The extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Purification by flash-column chromatography (SiO_2, hexanes/EtOAc, 5:1) gave **12** as a light yellow liquid (7.0 g, 60%): $R_f = 0.4$ (SiO_2, hexanes/EtOAc, 5:1); ^{1}H NMR (400 MHz,

$CDCl_3$): δ 7.27 (d, $J = 8.4$ Hz, 2H), 6.85 (d, $J = 8.4$ Hz, 2H), 5.14 (t, $J = 7.2$ Hz, 1H), 3.78 (s, 3H), 3.52 (s, 2H), 3.07 (dt, $J = 13.6$, 2.4 Hz, 2H), 2.33 (d, $J = 13.6$, 2H), 2.14 (d, $J = 7.2$ Hz, 2H), 1.91 (d, $J = 14.4$ Hz, 2H), 1.71 (s, 3H), 1.64–1.66 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 134.5, 133.4, 129.3, 118.6, 113.7, 55.3, 53.4, 44.5, 37.5, 36.5, 26.2, 23.6, 18.2. HRMS-ESI m/z $[M + H]^+$ calcd. for $C_{18}H_{28}NOS$: 306.1892; found 306.1887.

Tetrahydro-4-prenyl-2H-thiopyran-4-amine (13)

DDQ (227 mg, 1.0 mmol) was added to a solution of **12** (280 mg, 0.92 mmol) in CH_2Cl_2/H_2O (5:1; 18 mL). After stirring at rt overnight, the mixture was poured into saturated $NaHCO_3$ (40 mL). The organic components were extracted with CH_2Cl_2, and the extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash-column chromatography (SiO_2, hexanes/EtOAc/Et_3N, 10:10:1) gave **13** as a colorless liquid (119 mg, 70%): $R_f = 0.25$ (SiO_2, hexanes/EtOAc/Et_3N, 10:10:1); ^1H NMR (400 MHz, $CDCl_3$): δ 5.17 (tt, $J = 7.6$, 1.6 Hz, 1H), 2.84 (dt, $J = 10.8$, 3.6 Hz, 2H), 2.45 (dt, $J = 13.6$, 4.0 Hz, 2H), 2.02 (d, $J = 7.6$ Hz, 2H), 1.61–1.71 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.2, 118.5, 50.4, 42.2, 39.0, 26.1, 24.2, 18.1. HRMS-ESI m/z $[M + H]^+$ calcd. for $C_{10}H_{20}NS$: 186.1316; found 186.1320.

2,2-Dimethyl-3-iodo-8-thia-1-azaspiro[4.5]decane (14)

The solution of I_2 (650 mg, 2.6 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a solution of **13** (400 mg, 2.2 mmol) in CH_2Cl_2 (40 mL) and 15% $NaHCO_3$ (20 mL). After stirring at rt overnight, the reaction was quenched with sat. $Na_2S_2O_3$ (20 mL), and the mixture was extracted with CH_2Cl_2. The organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash-column chromatography (SiO_2, hexanes/EtOAc, 1:1) gave **14** as colorless thick oil (336 mg, 50%): $R_f = 0.5$ (SiO_2, hexanes/EtOAc, 1:1); ^1H NMR (400 MHz, $CDCl_3$): δ 3.85 (dd, $J = 7.2$, 4.4 Hz, 1H), 2.47–2.53 (m, 1H), 2.56–2.63 (m, 2H), 2.67–2.75 (m, 1H), 2.34 (dd, $J = 13.2$, 6.8 Hz, 1H), 2.11 (t, $J = 11.6$ Hz, 1H), 1.63–1.72 (m, 1H), 1.73–1.81 (m, 2H), 1.89–1.95 (m, 1H), 1.25 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 62.1, 60.1, 48.7, 42.5, 40.8, 34.6, 28.5, 28.0, 25.9, 25.8. HRMS-ESI m/z $[M + H]^+$ calcd. for $C_{10}H_{19}INS$: 312.0283; found 312.0282.

3-Azido-2,2-dimethyl-8-thia-1-azaspiro[4.5]decane (15)

NaN_3 (100 mg, 1.5 mmol) was added to the solution of **14** (320 mg, 1.0 mmol) in $MeOH/H_2O$ (4:1, 30 mL), and the mixture was heated to reflux for 12 h. After cooling to rt, MeOH was removed under reduced pressure. The remaining mixture was extracted with CH_2Cl_2 and dried over anhydrous Na_2SO_4. Purification by flash-column chromatography (SiO_2, hexanes/EtOAc, 1:1) gave **15** as a colorless thick oil (179 mg, 77%): $R_f = 0.35$ (SiO_2, hexanes/EtOAc, 1:1); ^1H NMR (400 MHz, $CDCl_3$): δ 3.62 (t, $J = 6.4$ Hz, 1H), 2.66–2.72 (m, 2H), 2.51–2.58 (m, 2H), 2.07 (dd, $J = 13.2$, 6.4 Hz, 1H), 1.71–1.82 (m, 4H), 1.86–1.89 (m, 1H), 1.16 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 70.0, 62.4, 58.6, 42.24, 42.20,

42.0, 29.7, 26.15, 26.10, 25.2. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{10}H_{19}N_4S$: 227.1330; found 227.1329.

3-Amino-2,2-dimethyl-8-thia-1-azaspiro[4.5]decane (1)

The solution of **15** (30 mg, 0.13 mmol) in anhydrous ethanol (10 mL) was stirred over 10% palladium on charcoal (0.01 g) under 1 atm of hydrogen gas overnight. The mixture was filtered through a celite pad, and the filtrate was concentrated under reduced pressure. The residue was purified by flash-column chromatography (SiO_2, CH_2Cl_2/MeOHEt_3N, 20:1:0.25) giving **1** as a thick colorless oil (24.7 mg, 95%): $R_f = 0.2$ (SiO_2, CH_2Cl_2/MeOH/Et_3N, 20:1:0.25); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.0 (dd, $J = 6.4$, 4.0 Hz, 1H), 2.48–2.70 (m, 4H), 2.02 (dd, $J = 12.8$, 6.8 Hz, 1H), 1.62–1.90 (m, 4H), 1.37 (dd, $J = 12.8$, 10 Hz, 1H), 1.10 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 60.6, 60.5, 50.4, 45.3, 42.9, 41.6, 29.1, 26.2, 26.1, 23.9. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{10}H_{21}N_2S$: 201.1425; found 201.1428.

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REFERENCES

1. Dake, G. Recent approaches to the construction of 1-azaspiro[4.5]decanes and related 1-azaspirocycles. *Tetrahedron* **2006**, *62*, 3467.
2. Sun, M.; Lu, H.; Wang, Y.; Yang, H.; Liu, H. Highly efficient formal synthesis of cephalotaxine, using the Stevens rearrangement–acid lactonization sequence as a key transformation. *J. Org. Chem.* **2009**, *74*, 2213.
3. Kawasaki, T.; Onoda, N.; Watanabe, H.; Kitahara, T. Total synthesis of (±)-cocculolidine. *Tetrahedron Lett.* **2001**, *42*, 8003.
4. Patil, A. D.; Freyer, A. J.; Reichwein, R.; Carte, B.; Killmer, L. B.; Faucette, L.; Johnson, R. K.; Faulkner, D. J. Fasicularin, a novel tricyclic alkaloid from the ascidian *Nephteis fasicularis* with selective activity against a DNA repair-deficient organism. *Tetrahedron Lett.* **1997**, *38*, 363.
5. Arimoto, H.; Asano, S.; Uemura, D. Synthesis of pinnaic acid: Asymmetric construction of spirocyclic core. *Tetrahedron Lett.* **1999**, *40*, 3583.
6. Kan, T.; Fujimoto, T.; Ieda, S.; Asoh, Y.; Kitaoka, H.; Fukuyama, T. Stereocontrolled total synthesis of potent immunosuppressant FR901483. *Org. Lett.* **2004**, *6*, 2729.
7. Abe, H.; Aoyagi, S.; Kibayashi, C. Total synthesis of the tricyclic marine alkaloids (–)-lepadiformine, (+)-cylindricine C, and (–)-fasicularin via a common intermediate formed by formic acid–induced intramolecular conjugate azaspirocyclization. *J. Am. Chem. Soc.* **2005**, *127*, 1473.
8. Hurley, T. B.; Peukert, S.; Wattanasin, S. Preparation of purrolecarboxamides and pyridinecarboxamides as inhibitors of undecaprenyl pyrophosphate synthase. *PCT Int. Appl.* WO 2008014311, **2008**.

9. Fischer, R.; Bretschneider, T.; Krueger, B.-W.; Santel, H. J.; Dollinger, M.; Erdelen, C.; Wachendorff-Neumann, U. Preparation of spirocyclic 1H-3-arylpyrrolidin-2,4-diones as pesticides. *Ger. Offen.* DE 4415334, 1995.
10. Diaba, F.; Puigbo, G.; Bonjoch, J. Synthesis of enantiopure 1-azaspiro[4.5]decanes by iodoaminocyclization of allylaminocyclohexanes. *Eur. J. Org. Chem.* **2007**, 3038.
11. Rule, N. G.; Detty, M. R.; Kaeding, J. E.; Sinicropi, J. A. Syntheses of 4H-thiopyran-4-one 1,1-dioxides as precursors to sulfone-containing analogs of tetracyanoquinodimethane. *J. Org. Chem.* **1995**, *60*, 1665.
12. Mazerolles, P.; Boussaguet, P.; Huc, V. 6-Chloro-1-hexene and 8-chloro-1-octene; *Org. Synth.*; John Wiley & Sons: London, 1999; vol. 76, p. 221.
13. Schkeryantz, J. M.; Woo, J. C. G.; Siliphaivanh, P.; Depew, K. M.; Danishefsky, S. J. Total synthesis of gypsetin, deoxybrevianamide E, brevianamide E, and tryprostatin B: Novel constructions of 2,3-disubstituted indoles. *J. Am. Chem. Soc.* **1999**, *121*, 11964.
14. Diaba, F.; Ricou, E.; Bonjoch, J. New insights into NIS-promoted aminocyclization: Synthesis of decahydroquinolines from 2-allylcyclohexylamines. *Org. Lett.* **2007**, *9*, 2633.
15. Bull, S. D.; Davies, S. G.; Fenton, G.; Mulvaney, A. W.; Prasad, R. S.; Smith, A. D. Chemoselective debenzylation of *N*-benzyl tertiary amines with ceric ammonium nitrate. *J. Chem. Soc., Perkin. Trans. 1* **2000**, 3765.
16. Knapp, S.; Levorse, A. T. Synthesis and reactions of iodo lactams. *J. Org. Chem.* **1988**, *53*, 4006.
17. Choi, Y.; George, C.; Strazewski, P.; Marquez, V. E. Synthesis of a conformationally locked version of puromycin amino nucleoside. *Org. Lett.* **2002**, *4*, 589.