Tetrahedron Letters 52 (2011) 1866–1870

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of 1-pyrroline 1-oxides analogous to pseudouridine

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ARTICLE INFO

Article history:
Received 27 October 2010
Revised 26 January 2011
Accepted 4 February 2011
Available online 4 March 2011

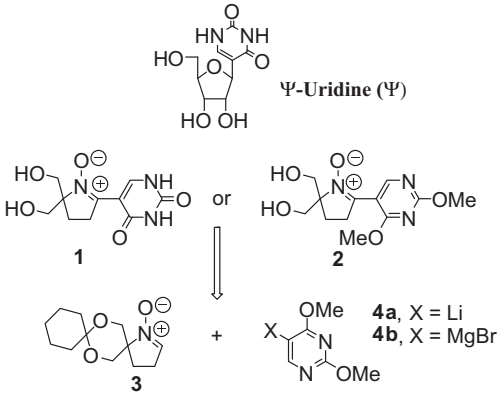
Keywords:
Pseudouridine
1-Pyrroline 1-oxides
Nitrones
C-Nucleoside analogues
Spin traps

ABSTRACT

Pseudouridine (ψ-uridine, Ψ) aza′-analogues with a 5,5-bis(hydroxymethyl)-1-pyrrolin-2-yl 1-oxide as the glycone mimic were obtained by the addition of (2,4-dimethoxypyrimidin-5-yl)magnesium bromide to 1-aza-7,14-dioxadispiro[4.2.5.2]pentadec-1-ene 1-oxide (**3**), followed by oxidation and removal of the protecting groups. The analogous synthesis from (2,4-dimethoxypyrimidin-5-yl)lithium and **3** was less efficient; in the first step of the reaction sequence, competing dimerisation of **3** predominated over addition of the organolithium agent to **3**.

Pseudouridine (ψ-uridine, Ψ, Scheme 1) is a natural *C*-nucleoside occurring in various types of RNA. It has been generally accepted that Ψ plays a significant role in fine-tuning of RNA functions and preservation of its structure during the translation process.[1] Moreover, the anti-mutagenic activity of Ψ against ionizing radiation or chemical mutagens, such as *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine or *N*-methyl-*N*-nitrosourea, has also been reported.[2] It has been suggested that its activity towards the chemical mutagens is due to the entrapment of free radicals derived from these mutagens.[3a] The biological significance of Ψ has stimulated many studies on the synthesis of Ψ analogues as potential antiviral and/or anticancer agents. Among the analogues, derivatives with an aza-heterocyclic mimic of the natural glycone have also been reported.[3] The following aza-heterocycles have been reported in the role of the glycone mimic: pyrrolidine,[3a–k] oxazole,[3l] isoxazole,[3m] isoxazoline,[3m] isoxazolidine,[3m,n] imidazolidine,[3o] thiazolidine[3p] or 1,2,4-oxadiazole.[3q] Among these aza-heterocyclic Ψ analogues, pyrrolidin-2-yl derivatives were examined for their anti-HIV activity[3a,b] or base-pairing properties,[3e–h] while analogues derived from oxazole,[3l] imidazolidine,[3o] or 1,2,4-oxadiazole[3q] were evaluated for their inhibitory potency towards some specific enzymes. The 1,2,4-oxadiazol-3-yl analogues showed inhibitory activity towards procollagen C-proteinase,[3q] whereas the imidazo-[1,2-*a*]pyridin-6-yl[4] analogues were active as reversible inhibitors of H^+/K^+ ATPase.

Herein, we report the synthesis of novel Ψ aza′-analogues with a 5,5-bis(hydroxymethyl)-1-pyrrolin-2-yl 1-oxide residue as the glycone mimic, i.e. compounds **1** and **2** (Scheme 1). These compounds possess a nitrone function that, in addition to the uracil moiety, may act as the biologically active site. Our interest in synthesizing these compounds was motivated by their possible application as novel free radical traps. Replacement of the ribose moiety by 1-pyrroline 1-oxide, a structural unit present in a number of efficient free radical traps,[5] would be expected to have an effect on the aforementioned anti-mutagenic properties of pseudouridine.[2] Furthermore, the additional hydroxymethyl group at the 5 position of the 1-pyrroline 1-oxide ring is expected to prevent the formation of final nitroxide-free radicals in the form of different stereoisomers, a potential complication in their spectroscopic studies resulting from the presence of asymmetric carbon centres in alternative nitroxide-free radicals with one hydroxymethyl group at this position.[6] Our research on the synthesis of



Scheme 1. Retrosynthesis of the Ψ-uridine analogues **1** and **2**.

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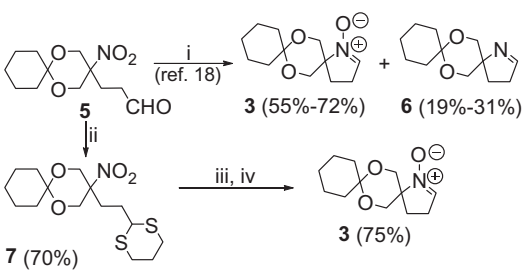
doi:10.1016/j.tetlet.2011.02.018

compounds **1** and **2** was also stimulated by reports on the therapeutic potential[7] of nitrones against diseases resulting from an imbalance between free radical formation and antioxidant production in the body, e.g. neurodegenerative diseases or cancer.[8] The literature revealed that the stable nitroxide-free radicals formed in this way protect cells against oxidative damage.[9] Syntheses and pharmacological properties of a number of nitrones with a heterocyclic substituent on the carbon atom of the nitrone function have been described.[5a,10] However, only a few examples of nitrones bearing a nucleobase moiety,[3l,m,11] or a nucleoside residue[12] have been reported. Recently, 5,5-dimethyl-2-(2′-deoxyuridin-5-yl)-1-pyrroline 1-oxide was reported, and postulated as a product of trapping of the 2′-deoxyuridin-5-yl radical derived from 5-halo-2′-deoxyuridines by 5,5-dimethyl-1-pyrroline 1-oxide (DMPO).[13] It was detected by HPLC/ESI-MS/MS and characterized by ^{1}H NMR spectroscopy. However, as reported in the original paper, it was not obtained on a preparative scale.

It is worth noting that nucleoside-derived free radicals (such as the 1′,2′-didehydro-2′-deoxyuridin-1′-yl radical) have attracted attention because of their postulated involvement in a variety of nucleic acid damage processes.[14]

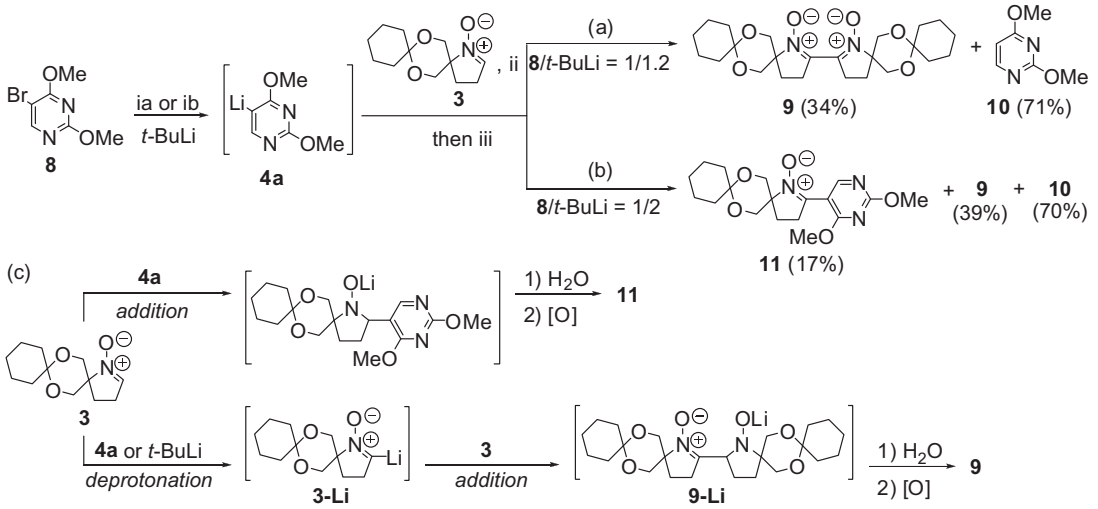
As mentioned previously, the literature data on nitrones with a uracil-5-yl residue is rather limited.[3l,3m,13] The reported *N*-(uracil-5-ylmethylene)methanamine *N*-oxide or *N*-(uracil-5-ylmethylene)benzylamine *N*-oxide was obtained from the addition of *N*-methyl- or *N*-benzylhydroxylamine, respectively, to uracil-5-carboxaldehyde.[3l,m] Our synthetic approach to **1** and **2** (Scheme 1) involves the addition of (2,4-dimethoxypyrimidin-5-yl)lithium (**4a**) or (2,4-dimethoxypyrimidin-5-yl)magnesium bromide (**4b**) to nitrone **3**, as the key step of the synthesis. Although heteroarylation of acyclic aldonitrones with lithiated heteroaryl compounds is of great importance in the synthesis of natural or biologically active compounds,[15] the literature data on the heteroarylation of 1-pyrroline 1-oxides is rather limited; heteroarylations with 3-lithiopyridine,[16a] 2-lithiothiazole,[16b] or 2-lithiofuran[16c] have been reported. To the best of our knowledge, **4a** and **4b**, or their *O*-alkylated counterparts, have not been examined in heteroarylations of acyclic or cyclic aldonitrones. Compound **4a**, or its *O*-alkylated counterparts, were employed in the syntheses of Ψ-uridine, its stereoisomers, or pyrrolidine analogues of Ψ-uridine.[3a–c,17]

Previously, compound **3** was prepared in this laboratory from γ-nitroaldehyde **5** under reductive conditions [Zn/AcOH/Py, Scheme 2, step (i)].[18] However, the formation of **6** as a by-product was also observed. The yield of **6** depended on the zinc dust source and varied from 19% to 31%. Isolation of the organic reaction products from colloidal zinc salts, and the subsequent separation of **3** from **6** by crystallization or column chromatography were difficult. Consequently, the yields of **3** were irreproducible and varied from 55% to 72%. The most recent reports on the preparation of 1-pyrroline 1-oxides reveal that the reduction of γ-nitroaldehydes with Zn still remains one of the most common methods for their preparation.[6,19,20] However, the yields of the final nitrones depend on the reaction conditions (and probably on the specific structure of the starting γ-nitroaldehydes): 82% ($Zn/HOAc/EtOH/H_2O$)[19a] or 9–50% ($MeOH/H_2O/NH_4Cl$).[6,19b,c] Additionally, purification of the target nitrones is rather complex. Based on reports on the synthesis of 5-(diethoxyphosphoryl)-5-methyl-1-pyrroline 1-oxide[21] (or its deuterated analogues[19a]) by oxidation of the pyrrolidine precursor (39–83%, depending on the oxidant used), we envisaged the preparation of **3** via a reaction sequence involving reductive cyclisation of **5**, followed by oxidation of the pyrrolidine intermediate. However, our preliminary trials revealed that protection of the formyl group was required prior to reduction of the nitro function to an amine. Thus we anticipated that the preparation of the starting pyrrolidine would require two additional steps, i.e. the aforementioned protection of the formyl group and then its deprotection after reduction of the nitro group. It was clear that the final yield of **3** using the envisaged method would be insufficient for preparative purposes. Therefore, in order to improve the preparation of **3**, we developed an alternative procedure which involved (Scheme 2): (a) conversion of **5** into thioacetal **7**[22] by the use of $HS(CH_2)_3SH/BF_3{\cdot}Et_2O$;[23] and (b) treatment of **7** with Al/Hg in a THF/water mixture, followed by treatment of the crude reaction product with $NaHCO_3$/MeI.[24] This procedure gave **3** in a total yield of 52%. From a preparative point of view, and compared to the reference method (i), this procedure gave reproducible results and avoided the difficult separation of **3** from the reaction mixture.



Scheme 2. Reagents and conditions: (i) Zn, AcOH, Py, EtOH, −5–3 °C, 3 h; (ii) $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C to rt, 2 h; (iii) Al/$HgCl_2$, THF, H_2O, rt, 2 h; (iv) $NaHCO_3$, MeI, MeCN, H_2O, 45 °C, 2 h.

Next, the reaction of **3** with (2,4-dimethoxypyrimidin-5-yl)lithium (**4a**) was examined (Scheme 3). Formation of **4a** from **8** or 5-iodo-2,4-dimethoxypyrimidine by the action of *n*-BuLi[3b,c,17a,25] or *t*-BuLi,[17g] has been reported. In light of the reports on the addition of *n*-BuLi to ketonitrones[26] (less active acceptors than aldonitrones), we decided to use *t*-BuLi to form **4a**. In contrast to *n*-BuLi, *t*-BuLi did not undergo the addition under the reported conditions.[16a] Our procedure involved: treatment of **8** (1 equiv) with *t*-BuLi [1.2 equiv, variant (ia); or 2 equiv, variant (ib)] at −78 °C; (ii) addition of **3** at −78 °C and stirring the reaction mixture at room temperature for 3 h, followed by removal of the volatiles; and (iii) treatment of the residue with $Cu(OAc)_2/NH_3$ (aq) at room temperature.[27] Variant (a) of this procedure, i.e. when **8** was treated with 1.2 equiv of *t*-BuLi in order to produce **4a**, gave 2,2′-binitrone **9** (34%) and **10** (71%). Variant (b), i.e. when **8** was reacted with 2 equiv of *t*-BuLi, afforded the desired compound **11** (17%) accompanied by **9** (39%) and **10** (70%).[28] The starting compound **3** was not recovered from the reaction mixtures. These results suggest that, in both variants of this reaction sequence, dimerisation of **3** predominated over the addition of **4a** to **3**. Presumably, the dimerisation was initiated by deprotonation of **3** at the 2 position by *t*-BuLi or **4a** (Scheme 3c). Addition of the resulting **3-Li** to **3**, followed by hydrolysis of **9-Li** and the subsequent oxidation furnished **9**. Dimer **9** was also obtained (31%) by the treatment of **3** (2 equiv) with *t*-BuLi (1 equiv) under the same conditions. In a separate experiment, when the reaction was quenched with wet Et_2O at −50 °C, prior to the oxidation step, TLC ($CHCl_3$/acetone, 85/15, v/v) showed the presence of both **3** and **9** in the reaction mixture; the mixture was not separated, and the ratio of **3**/**9** was not determined. These findings suggest that the reaction temperature was not a decisive factor in the formation of **9**. Such dimerisation of 1-pyrroline 1-oxides upon treatment with NaH (liquid NH_3), *n*-BuLi (−70 °C) or LDA (−70 °C) has been reported.[29] The literature revealed that the high reactivity of cyclic aldonitrones towards metalation at the nitrone carbon atom is a consequence of their fixed (*E*)-configuration. Stabilization of the organolithium carbanion (such as **3-Li**) by intramolecular coordination of lithium with the nitrone oxygen is postulated as a factor facilitating the metalation.[30] To the best our knowledge, competition between addition of an "external" nucleophile to an aldonitrone and dimerisation

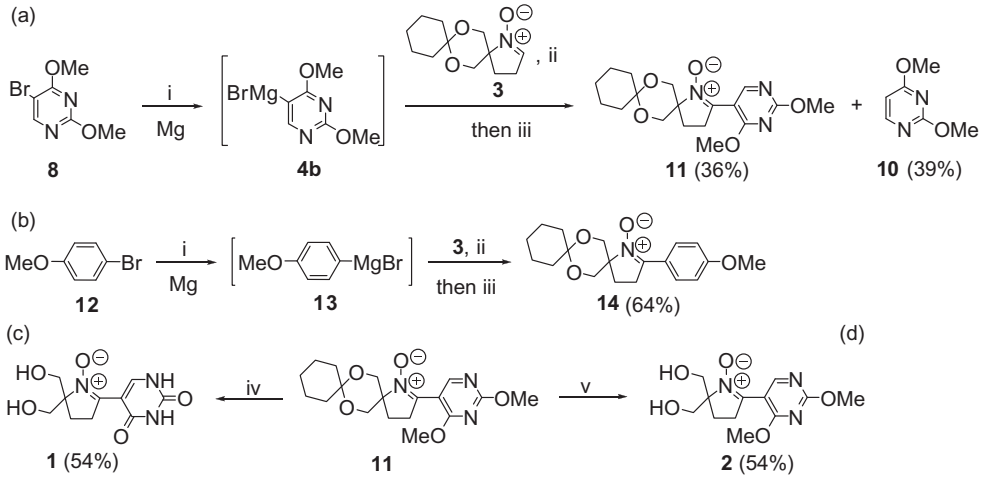


Scheme 3. Reagents and conditions: (i) *t*-BuLi (1.7 M solution in pentane), THF, −78 °C, 30 min: (a) **8**/*t*-BuLi = 1/1.2, (b) **8**/*t*-BuLi = 1/2; (ii) THF, −78 °C to rt, 3 h; (iii) $Cu(OAc)_2$, NH_3 (aq), 1,4-dioxane, CH_2Cl_2, rt, 1 d.

of this aldonitrone under the reaction conditions, such as that observed in the present studies, has not been discussed. Moreover, the same phenomenon has not been observed in the heteroarylation of 1-pyrroline 1-oxide-derived aldonitrones with 3-lithiopyridine, 2-lithiothiazole, or 2-lithiofuran,[16] although the reaction mixtures from some of these reactions were kept at room temperature prior to their work-up.[16c]

Since the previously obtained yield of **11** was not acceptable, the reaction of **3** with the organomagnesium reagent **4b** was performed (Scheme 4a). Derivative **4b** was prepared in THF from **8** and Mg in the presence of $(CH_2)_2Br_2$ under reflux.[31] An **8**/Mg/$(CH_2)_2Br_2$ molar ratio of 1/3/1.5 was required for the efficient conversion of **8** into **4b**.[32] The solution of **4b** was cooled to −10 °C and compound **3** was added. Then, the reaction mixture was stirred at room temperature for 2 h. Oxidation of the crude reaction product with $Cu(OAc)_2/NH_3$ (aq) was completed under the previously described conditions to afford **11** (36%) and **10** (39%); starting material **3** was not recovered.[33] The moderate yield of **11** could be explained in terms of steric effects on the addition of bulky **4b** to **3**. This assumption seems to be supported by the fact that the same reaction sequence with the use of **3** and (4-methoxyphenyl)magnesium bromide **13**, a less hindered organomagnesium agent than **4b**, gave **14** in 64% yield (Scheme 4b).[34] Finally, **11** was transformed into **1** (54%, Scheme 4c)[35] or **2** (54%, Scheme 4d)[36] by treatment with NaI/AcOH at 70 °C, or with AcOH at 80 °C, respectively.

In summary, compounds **1** and **2**, Ψ-uridine aza′-analogues with 5,5-bis(hydroxymethyl)-1-pyrrolin-2-yl 1-oxide as the glycone mimic, were readily obtained from the *O*,*O*′-cyclohexylidene-protected 5,5-bis(hydroxymethyl)-1-pyrroline 1-oxide (**3**) and (2,4-dimethoxypyrimidin-5-yl)magnesium bromide (**4b**) in three steps. The efficiency of the preparation of both **1** and **2** via the addition of (2,4-dimethoxypyrimidin-5-yl)lithium (**4a**) to **3** was modest, mainly due to competition between the addition of **4a** to **3** and the dimerisation of **3**. The presented approach can be considered as complementary to that based on the addition of hydroxylamines to carbonyl compounds. Our studies showed that it could be useful for the synthesis of keto-nitrones with the uracil-5-yl residue at the nitrone carbon atom. Further studies on the synthesis and biological properties of nucleoside analogues with a nitrone glycone, including examination of their ability to trap free radicals, are in progress.



Scheme 4. Reagents and conditions: (i) Mg, $(CH_2)_2Br_2$, THF, reflux, 3 h; (ii) THF: (a) −10 °C, 2 h; (b) rt, overnight; (iii) $Cu(OAc)_2$, NH_3 (aq), 1,4-dioxane, CH_2Cl_2, rt, 1 d; (iv) NaI, AcOH, 70 °C, 30 min; (v) AcOH, 80 °C, 30 min.

Acknowledgments

This work was financed by the Ministry of Science and Higher Education, Poland; projects 3 T09A 130 15, 1 T09B 013 30.

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22. *3-[2-(1,3-Dithian-2-yl)ethyl]-3-nitro-1,5-dioxaspiro[5.5]undecane* (**7**). $BF_3{\cdot}Et_2O$ (0.70 mL, 5.5 mmol) was added to a cold (0 °C) mixture of **5** (775 mg, 3.2 mmol), $HS(CH_2)_3SH$ (0.46 mL, 4.6 mmol) and dry CH_2Cl_2 (50 mL). After stirring for 2 h at room temperature, CH_2Cl_2 (50 mL) was added. The mixture was washed with NaOH aq (5%, 20 mL), H_2O (10 mL), brine (10 mL) and dried ($MgSO_4$). The volatiles were removed by distillation. Column chromatography of the residue (hexane/AcOEt, 3/1, v/v) gave **7** (775 mg, 70%) as a white solid (mp 124–128 °C). δ_H ($CDCl_3$, 200 MHz) 1.34–1.93 (13H, m), 1.97–2.17 (3H, m), 2.80–2.86 (4H, m), 3.89–3.96 (3H, m), 4.48 (2H, part of an AB quartet, $^2J_{AB}$ 12.8); δ_C ($CDCl_3$, 50 MHz) 22.50, 22.62, 25.52, 25.75, 28.67, 29.35, 30.10, 31.33, 35.10, 46.41, 63.28, 86.11, 99.33; ν_{max} (KBr) 2921, 2853, 1539, 1438, 1340, 1283, 1108, 941, 908; HRMS (EI, 70 eV) *m/z* calcd for $C_{15}H_{25}NO_4NaS_2$ $[M]^+$ 370.1117, found 370.1121.
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24. *1-Aza-7,14-dioxadispiro[4.2.5.2]pentadec-1-ene 1-oxide* (**3**). A mixture of aluminium foil (Roth GmbH; 1.5 g, 57.5 mmol), dry THF (100 mL) and $HgCl_2$ (1.5 g, 6.0 mmol) was stirred at room temperature for 10 min under argon. A solution of **7** (1.0 g, 2.9 mmol) in a THF/H_2O mixture (50 mL/2 mL) was added dropwise. The reaction mixture was stirred at room temperature until **7** was not detected by TLC (hexane/AcOEt, 3/1, v/v), ca. 2 h, and then filtered through a Celite® pad. The filtrate was concentrated to dryness and the residue (810 mg) dissolved in MeCN (250 mL). $NaHCO_3$ aq (saturated, 40 mL) and MeI (16.2 mL, 0.24 mol) were added. The mixture was stirred at 45 °C for 2 h, cooled to room temperature and diluted with CH_2Cl_2 (300 mL). The mixture was washed with H_2O (80 mL), brine (80 mL) and dried ($MgSO_4$). The volatiles were removed by distillation. Crystallization of the residue (hexane/AcOEt) gave **3** (485 mg, 75%) as a white solid (mp 124–126 °C). The NMR spectra were consistent with those described in Ref. 18.
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28. *2,2′-Bi(7,14-dioxa-1-aza-dispiro[4.2.5.2]pentadec-1-ene) 1,1′-dioxide* (**9**) *and 2-(2,4-dimethoxypyrimidin-5-yl)-7,14-dioxa-1-azadispiro[4.2.5.2]pentadec-1-ene 1-oxide* (**11**). *t*-BuLi (Aldrich; 1.7 M soln in pentane, 1.1 mL) was added to a mixture of **8** (Aldrich; 200 mg, 0.9 mmol) and dry THF (2 mL) at −78 °C under argon. The mixture was left at −78 °C for 30 min and then compound **3** (190 mg, 0.8 mmol) was added. The mixture was allowed to warm to room temperature. The reaction was followed by TLC ($CHCl_3$/acetone, 85/15, v/v) at 30 min intervals. After stirring for 3 h at room temperature, when **3** was no longer detected by TLC, Et_2O (20 mL) was added. The mixture was washed with H_2O (5 mL) and evaporated to dryness. The residue was dissolved in 1,4-dioxane (6 mL) and CH_2Cl_2 (2 mL). $Cu(OAc)_2$ (40 mg), NH_3 (aq) (0.3 mL) and H_2O (1 mL) were added. The mixture was stirred at room temperature for 1 d. The organic layer was separated, washed with H_2O (10 mL), dried ($MgSO_4$) and concentrated to dryness. Column chromatography of the residue ($CHCl_3$/acetone, 85/15, v/v) gave **9** (70 mg, 39%), **10** (89 mg, 71%), and **11** (50 mg, 17%). **9**: A white solid (mp >180 °C, dec). δ_H ($CDCl_3$, 200 MHz) 1.43–1.56 (16H, m), 1.90 (4H, m), 2.35 (4H, m), 3.29 (4H, m), 3.56 and 4.34 (8H, AB quartet, $^2J_{AB}$ 11.4 Hz); δ_C ($CDCl_3$, 50 MHz) 22.34, 22.58, 25.42, 26.16, 27.48, 28.49, 36.98, 64.28, 66.43, 72.57, 98.80, 136.38; ν_{max} (KBr) 2936, 2860, 1496, 1448, 1380, 1240, 1156, 1044, 920; HRMS (EI, 70 eV) *m/z* calcd for $C_{24}H_{36}O_6N_2$ (M^+) 448.2573, found 448.2557. **11**: A white solid (mp 151–152 °C). δ_H ($CDCl_3$, 200 MHz) 1.34–1.84 (8H, m), 2.1 (2H, m), 2.39 (2H, m), 3.12 (2H, m), 3.63 and 4.57 (4H, AB quartet, $^2J_{AB}$ 11.4), 4.00 (3H, s), 4.02 (3H, s), 10.09 (1H, s); δ_C ($CDCl_3$, 50 MHz) 22.39, 22.67, 25.49, 27.42, 28.21, 28.84, 37.29, 54.21, 55.19, 64.36, 72.23, 98.77, 105.98, 136.72, 159.26, 165.04, 167.74; ν_{max} (KBr) 2948, 2936, 1716, 1688, 1556, 1536, 1480, 1464, 1356, 1252, 1244, 1108; HRMS (EI, 70 eV) *m/z* calcd for $C_{18}H_{25}O_5N_3$ (M^+) 363.1794, found 363.1812. The NMR spectra of **10** were consistent with those described: Pelissier, H.; Rodriguez, J.; Volhardt, K. P. C. *Chem. Eur. J.* **1999**, *5*, 3549.
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31. For generation of the 2,4-dimethoxypyrimidine-Grignard reagent by halogen-metal exchange, see Ref. 3b.

32. Presumably, the formation of **4b** was facilitated by $MgBr_2$ formed from Mg and $(CH_2)_2Br_2$. $MgBr_2$ could play a similar role as LiCl in the preparation of Grignard reagents from both arylmagnesium chlorides and bromides, see: (a) Piller, F. M.; Metzger, A.; Schade, M. A.; Hagg, B. A.; Gavryushin, A.; Knochel, P. *Chem. Eur. J.* **2009**, *15*, 7192; (b) Yamada, S.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 2215.
33. *2-(2,4-Dimethoxypyrimidin-5-yl)-7,14-dioxa-1-azadispiro[4.2.5.2]pentadec-1-ene 1-oxide* (**11**). $(CH_2)_2Br_2$ was added in 5 portions (60 μl per 30 min, 3.5 mmol) to a refluxed mixture of **8** (500 mg, 2.3 mmol), Mg (168 mg, 6.9 mmol) and dry THF (10 mL) under argon. When **8** had disappeared (TLC, hexane; after ca. 3 h), the mixture was cooled to −10 °C and compound **3** (339 mg, 1.5 mmol) was added. After stirring for 2 h at −10 °C, the mixture was allowed to warm to room temperature, stirred overnight and filtered through a Celite® pad. The filtrate was concentrated to dryness. The residue was treated with $Cu(OAc)_2$/NH_3 (aq) under the conditions described in Ref. 28. Column chromatography ($CHCl_3$/acetone, 85/15, v/v) gave **10** (126 mg, 39%) and **11** (197 mg, 36%, mp 151–152 °C).
34. *2-(4-Methoxyphenyl)-7,14-dioxa-1-azadispiro[4.2.5.2]pentadec-1-ene 1-oxide* (**14**) was obtained from **3** (2.0 g, 8.8 mmol) and **12** (10 g, 53.5 mmol) under the conditions described in Ref. 33. Crystallization (AcOEt) gave **14** (1.9 g, 64%) as a white solid (mp 180–183 °C). δ_H ($CDCl_3$, 200 MHz) 1.46–1.62 (8H, m), 2.02–2.10 (2H, m), 2.44 (2H, m), 3.06 (2H, m), 3.65 and 4.63 (4H, AB quartet, $^2J_{AB}$ 11.4), 3.84 (3H, s), 6.94 (2H, m), 8.32 (2H, m); δ_C ($CDCl_3$, 50 MHz, APT) positive amplitude: 22.42, 22.69, 25.52, 26.96. 27.44, 37.36, 64.52, 73.12, 98.73, 121.64, 140.12, 161.38; negative amplitude: 55.33, 113.83, 129.66; ν_{max} (KBr) 2990, 1568, 1450, 1376, 1286, 1159, 1012; HRMS (EI, 70 eV) *m/z* calcd for $C_{19}H_{25}O_4N$ (M^+) 331.1783, found 331.1780.
35. *2-(1H,3H-Pyrimidin-2,4-dione-5-yl)-5,5-bis(hydroxymethyl)-1-pyrroline 1-oxide* (**1**). A mixture of **11** (80 mg, 0.2 mmol), NaI (80 mg) and AcOH (3 mL) was heated at 70 °C for 30 min. The volatiles were removed by distillation. The residue was dissolved in MeOH (5 mL) and neutralized with solid K_2CO_3. The mixture was evaporated to dryness. Column chromatography of the residue (acetone/MeOH, 9/1, v/v) gave **1** (32 mg, 54%) as a white solid (mp >170 °C, dec). δ_H (CD_3OD, 200 MHz) 2.24 (2H, m), 3.20 (2H, m), 3.50 and 3.91 (4H, AB quartet, $^2J_{AB}$ 11.6), 9.93 (1H, s); δ_C (CD_3OD, 50 MHz) 22.77, 30.91, 63.30, 83.07, 98.33, 104.92, 143.98, 146.36, 152.58, 164.31; ν_{max} (KBr) 3260, 1716, 1668, 1592, 1496, 1436, 1224, 1192, 1024; HRMS (EI, 70 eV) *m/z* calcd for $C_{10}H_{13}O_5N_3$ (M^+) 255.0855, found 255.0853.
36. *2-(2,4-Dimethoxypyrimidin-5-yl)-5,5-bis(hydroxymethyl)-1-pyrroline 1-oxide* (**2**) was obtained by treating **11** (120 mg, 0.3 mmol) with AcOH (5 mL) at 80 °C for 30 min. The reaction mixture was worked up in the same way as described in Ref. 35. Column chromatography ($CHCl_3$/MeOH, 9/1, v/v) gave **2** (50 mg, 54%) as a colourless oil. δ_H ($CDCl_3$, 200 MHz) 2.06–2.14 (2H, m), 3.14 (2H, m), 3.73 (2H, part an AB quartet, $^2J_{AB}$ 11.2), 4.05 (8H, m), 9.98 (1H, s); δ_C ($CDCl_3$, 50 MHz, APT) positive amplitude: 23.24, 30.64, 64.48, 80.20, 96.97, 105.46, 123.72, 165.26, 168.05; negative amplitude: 54.27, 55.22, 143.33; ν_{max} (KBr) 3356, 2960, 2936, 1588, 1548, 1488, 1468, 1392, 1360, 1192, 1088, 1048, 1016; HRMS (EI, 70 eV) *m/z* calcd for $C_{12}H_{17}O_5N_3$ (M^+) 283.1168, found 283.1172.