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Probing the reactivity of nebularine *N*1-oxide. A novel approach to C-6 *C*-substituted purine nucleosides

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ABSTRACT

A novel approach to the synthesis of purine nucleoside analogues, featuring the reaction of the C6–*N*1–O$^-$ aldonitrone moiety of 9-ribosyl-purine (nebularine) *N*1-oxide with some representative dipolarophiles, as well as Grignard reagents, is reported. Addition of Grignard reagents to the electrophilic C-6 carbon of the substrate allows a facile access to C-6 *C*-substituted purine nucleosides without using metal catalysts. 1,3-Dipolar cycloaddition processes lead to novel nucleoside analogues via opening, degradation or ring-enlargement of the pyrimidine ring of the base system of the first-formed isoxazoline or isoxazolidine cycloadduct.

1. Introduction

In the last decades many research groups have focused their attention to the preparation of new modified nucleosides and nucleotides with the aim of expanding the pool of molecules with potential antineoplastic, antihypertensive and antiviral activities.[1] In this context, efforts have been directed to the synthesis of sugar[2] and/or base[3]-modified nucleosides. A large number of nucleobase analogues exist and several nucleoside analogues have been employed against cancer and viral diseases. In addition, base-modified nucleosides often show fluorescent properties,[4] and can be used as fluorescent probes for the analysis of DNA and RNA structures as well as for analysing the interaction of DNA and RNA with binding proteins. Purine bases and nucleosides bearing a C- or *N*-substituent at C-6 represent an important class of compounds possessing a broad spectrum of biological effects including cytostatic, antiviral, antibacterial as well as receptor–modulation activity.[5] The reactivity imparted to purines and related nucleosides by halogenation at C-6 has opened the way to the construction of new libraries of C-6 modified nucleosides generally through direct aromatic nucleophilic substitution (S_NAr),[6] or metal-mediated cross-coupling processes[3a,7] (Fig. 1). The most reliable methods to access C-6 *C*-substituted nucleosides use metal or organometal-mediated reactions.[3a] However, there is still a great need for the development of new methods for the introduction of *C*-substituents at C-6.

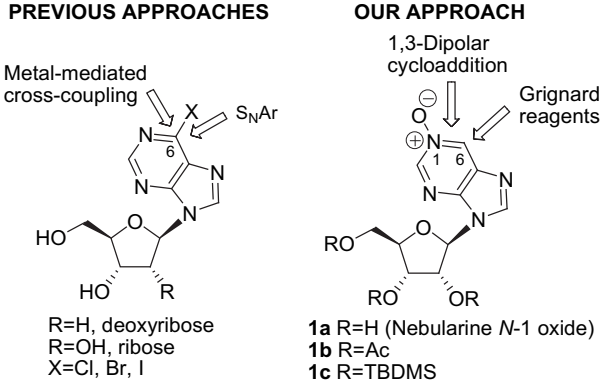

Fig. 1. Approaches to C-6 functionalization of purine nucleosides.

Nitrones are precious substrates used in organic synthesis for the assembly of structurally complex nitrogen-containing compounds. Their most well-studied reactions are the 1,3-dipolar cycloadditions (1,3-DC) and the nucleophilic addition of organometallic reagents.[8] We reasoned that 9-ribosyl-purine (nebularine) *N*1-oxide (**1a**, Fig. 1), embodying a potentially reactive C6–*N*1–O$^-$ nitrone moiety, could allow the C-6 functionalization of the purine base. To probe this concept the reactivity of sugar-protected **1b** and **1c** (Fig. 1) towards some representative

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dipolarophiles as well as Grignard reagents, respectively, was explored. The results obtained are described in the present paper.

2. Results and discussion

2′,3′,5′-Tri-*O*-acetyl-nebularine *N*1-oxide (**1b**, Fig. 1) was used as starting material for 1,3-DC processes whereas 2′,3′,5′-tri-*O*-(*tert*-butyldimethylsilyl)-nebularine *N*1-oxide (**1c**, Fig. 1) was employed to test the addition of Grignard reagents. Compounds **1b** and **1c** were synthesised from 2′,3′,5′-tri-*O*-acetyl-nebularine and 2′,3′,5′-tri-*O*-(*tert*-butyldimethylsilyl)-nebularine, respectively,[9] by reaction of nebularine with catalytic amounts of methyltrioxorhenium ($MeReO_3$) in the presence of H_2O_2, as described in the literature for the preparation of the corresponding purine *N*1-oxide.[10] Though the cycloaddition of aromatic *N*-oxides of various heterocyclic systems has extensively been investigated,[11] to our knowledge no report exists in the literature on the reactivity of *N*-oxides of purine nucleosides in cycloaddition reactions.

Reaction of compound **1b** with some representative dipolarophiles was carried out as shown in Table 1 and Scheme 1, to give the novel nucleoside analogues **2** and **4**–**7**, the structure of which was determined by high-field 2D-NMR analyses. As expected,[12] in all the analysed cases, we observed that the first-formed isoxazoline or isoxazolidine adduct did not survive. Therefore, the nucleoside products obtained from such processes are all derived from the cleavage of the N1–O bond in the cycloadduct followed in some cases by further evolution of the first-formed C-6 substituted purine system. In particular, reaction of **1b** with an equimolar amount of dimethyl acetylenedicarboxylate in THF gave the two unusual nucleoside analogues **2** (25%) and **4** (40%) (Table 1, entry 1) possessing modified heterocyclic base systems. Compound **2** proved unstable as such giving a mixture of partially deacetylated products on standing. However, its fully deacetylated derivative **3**, obtained by treatment of **2** with NH_4OH (concd) in MeOH, was a stable product, which was used for NMR characterisation. Compound **4** contains the 5:7-fused imidazo[4,5-*d*][1,3]diazepine ring system. The ^1H NMR spectrum of **4** recorded in CD_3OD showed it to be a mixture of two tautomers in a 7:3 ratio. 2D-NMR studies carried out in this solvent gave no conclusive evidences on the structure of **4** that was eventually solved by performing NMR analyses in DMSO-d_6 where the major tautomer **4** was present in 88% amount. Few examples of nucleoside analogues based on this base framework (ring-expanded nucleosides, RENs) exist all displaying significant biological activities.[13] The interest towards this type of substances is keen and the facile access to this framework is particularly appealing. In particular, compound **4** is the first example of a C-7 analogue of coformycin,[13c] (Fig. 2) a highly potent inhibitor of adenosine deaminase (ADA), an enzyme playing a key role in purine metabolism.[14]

Table 1
Reaction of **1b** with dipolarophiles

Entry	Dipolarophile	Conditions (solvent)	Products (yield %)
1	Dimethyl acetylenedicarboxylate	rt, 2 h (THF)	**2** (25%), **4** (40%)
2	3-Phenyl-2-propynenitrile	rt, 16 h (THF)	NR
3	3-Phenyl-2-propynenitrile	Reflux, 4 h (dioxane)	**5** (45%), **6** (30%)
4	*N*-Methylmaleimide	rt, 5 h or reflux, overnight (THF)	NR
5	*N*-Methylmaleimide	Reflux, 5 h, (dioxane/toluene, 1:1)	**7** (60%)
6	Diphenylacetylene	Reflux, overnight (THF or dioxane)	NR
7	Dimethyl maleate or dimethyl fumarate	Reflux, overnight (toluene)	NR

NR: no reaction.

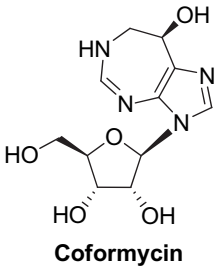
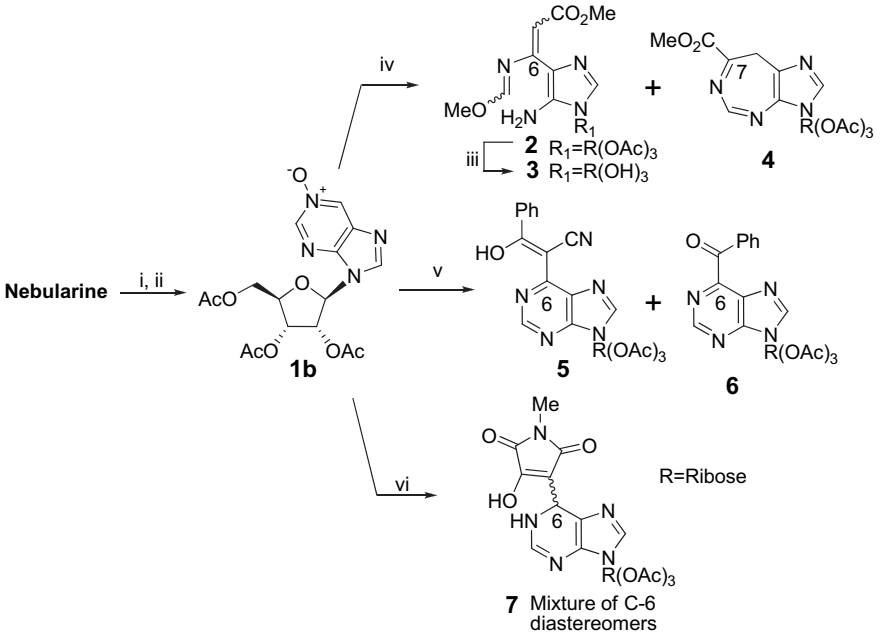
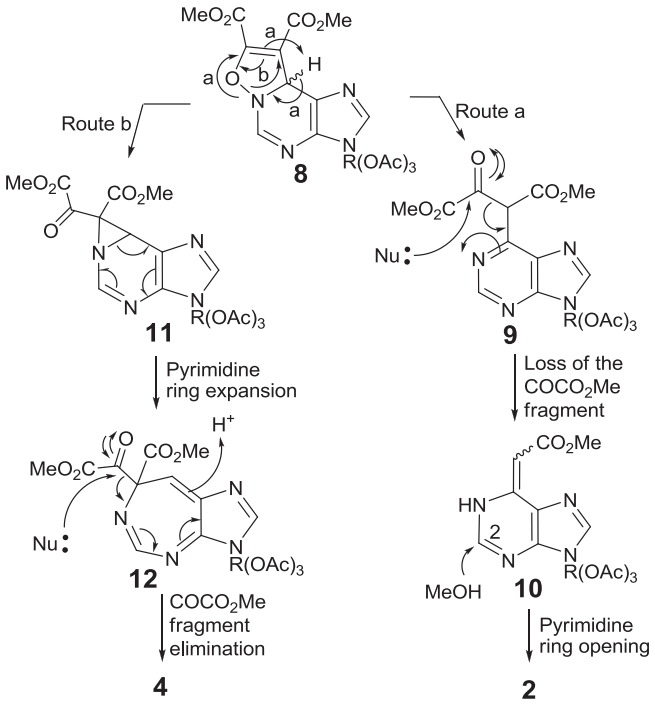


Fig. 2. Structure of coformycin.



Scheme 1. Reaction of **1b** with dipolarophiles: i. Ac_2O/pyridine;[9] ii. $MeReO_3$–H_2O_2 (30% aq), MeOH, rt, overnight (80% over two steps); iii. NH_4OH (concd)–MeOH, rt, 30 min; iv. Dimethyl acetylenedicarboxylate, THF, rt, 2 h; v. 3-phenyl-2-propynenitrile, dioxane, reflux, 4 h; vi. *N*-methylmaleimide, dioxane/toluene (1:1), reflux, 5 h.

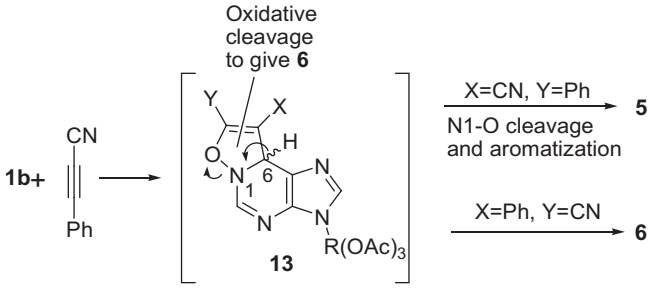
A tentative explanation for the formation of **2** and **4** is depicted in Scheme 2. Generation of their base system calls for the extrusion of a two-carbon fragment from the initially-formed isoxazoline adduct **8**. In particular, formation of **2** can be explained via isoxazoline opening with concomitant base aromatization, to give the C-6 substituted species **9** (route a) followed by loss of a CO–CO_2Me fragment with formation of a two-carbon chain at C-6 (**10**).[12] Evolution of **9** towards the conjugated species **10** via attack of a nucleophile at the ketone carbonyl seems logical and would well explain formation of the exocyclic double bond in **10**. Transformation of dimethyl α-ketosuccinates, such as **9** into methyl acetates by loss of this structural fragment has previously been reported.[15] The electron-withdrawing effect of the exocyclic unsaturated ester moiety in the latter may then be responsible for the opening of the pyrimidine ring through attack of MeOH at C-2, possibly in the work-up and/or purification step, to eventually give **2**. This type of reactivity at C-2 in **10** is strongly reminiscent of that exhibited by the *N*1-2,4-dinitrophenyl-inosine derivatives, previously studied in our group, leading to formation of AICAR derivatives.[16] The imidazo 4-substituted framework of **2** is unprecedented.



Scheme 2. A mechanistic hypothesis for the formation of **2** and **4**.

As for compound **4**, Stauss et al.[17] reported formation of 2-methyl-4-phenyl-5*H*-benzo[*d*][1,3]diazepin-5-carboxylic acid esters as by-products of the reaction of 2-methyl-4-phenyl-quinazoline 3-oxide with dimethyl and diethyl acetylenedicarboxylates and a plausible mechanistic hypothesis was given for the reaction path leading to the benzodiazepine system. In particular, formation of a cyclopropane-containing intermediate was postulated to be responsible for the pyrimidine ring enlargement. In a similar way, it is conceivable that the seven-membered ring in **4** can originate from the electrocyclic opening of an aziridine-containing intermediate (**11**, Scheme 2), in turn formed by the fragmentation/rearrangement of the initial adduct **8** (route b). The ring-enlarged compound **12** would once again undergo elimination of the α-ketoester side-chain possibly via nucleophilic attack at the ketone carbonyl during work-up.

Non-symmetric 3-phenyl-2-propynenitrile failed to react with **1b** at room temperature in THF (Table 1, entry 2) but gave a mixture of C-6 substituted nucleosides **5** (45%) and **6** (30%) when the process was conducted in dioxane at reflux (entry 3). Compound **5** is likely derived from the opening of isoxazoline ring in one of the two expected diastereomeric adducts **13** (Scheme 3) induced by loss of the C6-H proton and aromatization of the heterocyclic system. On the other hand, it seems hazardous trying to hypothesize a mechanistic route to C-6 benzoylated **6**. However, it can be envisaged that the oxidative cleavage of the double bond in the other adduct (**13**, X=Ph, Y=CN), with loss of a two-carbon fragment and aromatization, should occur to generate **6**. As far as we know, the direct introduction of acyl substituents at C-6 of the purine nucleoside system has never been reported before, and this type of substances is still rather rare.



Scheme 3. A mechanistic hypothesis for the formation of **5** and **6**.

Early attempts to induce reaction of **1b** with *N*-methylmaleimide in THF, both at room temperature and at reflux (Table 1, entry 4), were unsuccessful. However, when the process was carried out in dioxane/toluene (1:1) at reflux (entry 5) the C-6 derivative **7** was obtained in a 60% yield as a 1:1 mixture of diastereomers, once again through isoxazoline opening and oxidation at the maleimide portion. The ratio of isomers in the initially-formed mixture varied with HPLC purification (silica column) and/or on standing up to ca. 1:2, likely as a consequence of the acidity of the C-6 proton next to the maleimide moiety. NMR data could not provide unambiguous evidence on which is the major diastereomer. Considering that the maleimide portion in **7** is susceptible to further synthetic modifications,[18] access to C-6 maleimido-derivatives, such as **7** opens the way to the preparation of more complex and functionalised C-6 nucleoside derivatives. Maleimido- or *N*-methylmaleimido-containing substances, both of natural and non-natural origin, usually display significant biological properties. For example, showdomycin[19] is a potent nucleoside antibiotic isolated from *Streptomyces showdoensis*, while bisindolylmaleimides are known to be potent protein kinase C (PKC) inhibitors.[20]

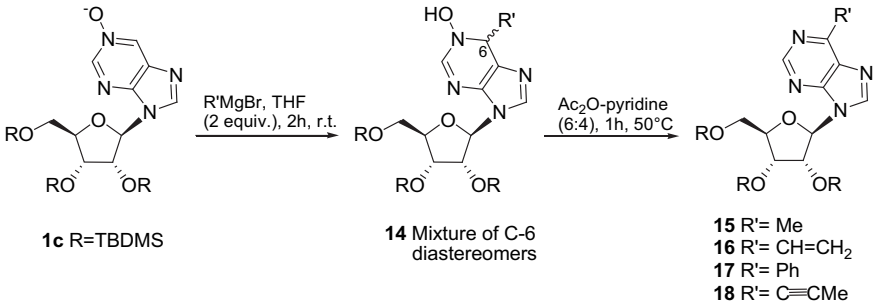
Finally, diphenylacetylene failed to react with **1b** also on prolonged reflux both in THF and dioxane (Table 1, entry 6). Similar results were obtained with dimethyl maleate and dimethyl fumarate on reflux in toluene, also using excess reagents (Table 1, entry 7). The above results showed that nebularine oxide derivative **1b** displays the characteristic reactivity of nitrones towards electron-poor dienophiles.

To further test the nitrone reactivity showed by **1a**, we next investigated the reaction of sugar-silylated **1c** with some representative Grignard reagents. It is known that nitrones smoothly undergo nucleophilic addition of organometallic reagents. Indeed, treatment of **1c** with a 2-fold excess of a Grignard reagent afforded the C-6 *C*-substituted *N*1-hydroxy adducts **14** as single products (Table 2 and Scheme 4). These substances slowly decomposed on standing, partly giving dehydration to C-6 substituted nebularine derivatives **15**–**18**. This process was pushed towards the latter

substances in nearly quantitative yields, by treatment of the crude C6-adducts with Ac_2O in pyridine (6:4) at 50 °C. Formation of **15**–**18** indicated, as reported in the literature,[21] the more electrophilic nature of the C-6 atom of the nucleobase when compared to the C-2 atom. The structure of the obtained compounds was ascertained by high-field 2D NMR and comparison with literature data (see Experimental section).

Table 2
Reaction of **1c** with Grignard reagents

Entry	Grignard reagent (equiv)	Conditions (solvent)	Products (yield%, over two steps)
1	Methylmagnesium bromide (2)	rt, 2 h (THF)	**15** (82%)
2	Vinylmagnesium bromide (2)	rt, 2 h (THF)	**16** (71%)
3	Phenylmagnesium bromide (2)	rt, 2 h (THF)	**17** (82%)
4	Propinylmagnesium bromide (2)	rt, 2 h (THF)	**18** (80%)



Scheme 4. Reaction of **1c** with representative Grignard reagents.

Overall, reaction of **1c** with Grignard reagents is of general applicability, working well with various types of substituents on the organometallic partner, leading to compounds **15**–**18** in good yields comparable[22] to, or better[7,23] than, those reported in the literature. It is worth noting that our process allows the direct introduction of a *C*-substituent on C-6 without using a metal catalyst. Based on both the facile reaction and purification procedures it is conceivable that the process can be easily performed on gram scale opening the way to obtain large amounts of C-6 *C*-substituted nucleosides without employing different reaction conditions.

3. Conclusions

In conclusion, an unprecedented approach to the C-6 C-functionalization of the purine nucleoside base system has been explored. In some cases, 1,3-DC reactions led to unexpected, structurally intriguing, products through new reaction pathways. Studies are in progress to investigate the scope of the described processes as well as to further explore the synthetic potential of nebularine *N*1-oxide. Since purine nucleosides, such as **14**, embodying the 6,9-dihydro-1*H*-purin-1-ol moiety are unprecedented, future efforts will also focus on using these addition products to prepare nucleoside analogues possessing novel modifications on the base system. We believe that the developed procedures may have future synthetic applications.

4. Experimental section

4.1. General methods

All reagents were obtained from commercial sources (Sigma–Aldrich) and were used without further purification. ^1H and ^{13}C NMR spectra were performed on a Varian Mercury Plus 400 MHz and Varian Unity Inova 700 MHz in $CDCl_3$, CD_3OD or DMSO-d_6 solvents. Chemical shifts are reported in parts per million (δ) relative to the residual solvent signals: $CHCl_3$ 7.27, CD_2HOD 3.31, CD_2HSOCD_3 2.49 for ^1H NMR; $CDCl_3$ 77.0, CD_2HOD 49.0, CD_2HSOCD_3 39.5 for ^{13}C NMR. ^1H NMR chemical shifts were assigned by 2D-NMR experiments. The abbreviations s, br s, d, dd and m stand for singlet, broad singlet, doublet, doublet of doublets and multiplet, respectively. HPLC analyses and purifications were carried out on a Jasco UP-2075 Plus pump equipped with a Jasco UV-2075 Plus UV detector using a 4.60×150 mm LUNA (Phenomenex) silica column (particle size 5 μm) eluted with a linear gradient of AcOEt in hexane (from 50 to 100% in 30 min, flow 1.0 mL min^{-1}, system A; from 80 to 100% in 30 min, flow 1.0 mL min^{-1}, system B; from 50 to 100% in 60 min, flow 1.0 mL min^{-1}, system C) or using a 4.8×150 mm C-18 reverse-phase column (particle size 5 μm) eluted with a linear gradient of MeOH in H_2O (from 0 to 100% in 60 min, flow 1.0 mL min^{-1}, system D). UV spectra were recorded on a Jasco V-530 UV spectrophotometer. High Resolution MS spectra were recorded on a Bruker APEX II FT-ICR mass spectrometer using electrospray ionization (ESI) technique in positive mode. IR spectra were recorded on a Jasco FT-IRFTIR 430 spectrophotometer. Optical rotations were determined on a Jasco polarimeter using a 1 dm cell at 20 °C; concentrations are in g/100 mL. Column chromatography was performed on silica gel (Merck, Kieselgel 60, 0.063–0.200 mm). Analytical TLC analyses were performed using F_{254} silica gel plates (0.2 mm, Merck). TLC spots were detected under UV light (254 nm).

4.2. Synthesis of 2′,3′,5′-tri-*O*-acetyl-nebularine *N*1-oxide (1b)

Nebularine was acetylated overnight with Ac_2O–pyridine under standard conditions to give essentially pure triacetate. A mixture of $MeReO_3$ (5 mg, 0.02 mmol) and 30% aqueous H_2O_2 (0.4 mL, 4.0 mmol) in methanol (6 mL) was stirred at room temperature for 10 min. Then crude 2′,3′,5′-tri-*O*-acetyl-nebularine (378 mg, 1.0 mmol) in methanol (4 mL) was added dropwise while stirring. Stirring was continued at room temperature overnight. Then the solvent was removed under reduced pressure and the crude was purified on a silica gel column eluted with increasing amounts of MeOH in $CHCl_3$ (from 0 to 10%) to afford pure 2′,3′,5′-tri-*O*-acetyl-nebularine *N*1-oxide **1b** (315 mg, 80% over two steps).

Compound **1b**: white foam; $[\alpha]_D^{20}$ −16.1 (*c* 0.13, CH_3OH), ^1H NMR (400 MHz, CD_3OD) δ_H 9.16 (d, *J*=1.8 Hz, 1H), 9.04 (d, *J*=1.8 Hz, 1H), 8.76 (s, 1H), 6.34 (d, *J*=5.0 Hz, 1H), 6.03–5.98 (m, 1H), 5.69–5.65 (m, 1H), 4.52–4.48 (m, 1H), 4.44 (dd, *J*=12.2, 3.5 Hz, 1H), 4.39 (dd, *J*=12.2, 4.9 Hz, 1H), 2.14 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ_C 172.1, 171.3, 171.1, 150.5, 146.4, 145.3, 139.3, 135.5, 88.5, 81.7, 74.2, 71.7, 64.0, 20.6, 20.4, 20.2; *m*/*z* (HRESIMS)

395.1212 ([M+H]$^+$, $C_{16}H_{19}N_4O_8$, requires 395.1203); IR (neat) ν_{max} 1748, 1495, 1424, 1369, 1229 cm^{-1}; UV (MeOH) λ_{max} 242, shoulder 267 nm.

4.3. Reaction of 1b with dimethyl acetylenedicarboxylate. Synthesis of 2–4

A solution of **1b** (50 mg, 0.13 mmol) and dimethyl acetylenedicarboxylate (18 mg, 0.13 mmol) in dry THF (2.5 mL) was stirred at room temperature. After 2 h the process was complete (TLC monitoring, AcOEt/MeOH, 95:5) and the solvent was evaporated under reduced pressure. The crude was purified on a silica gel column eluted with increasing amounts of MeOH in AcOEt (from 0 to 20%) affording two main products: compound **2** (16 mg, 25%) and **4** (23 mg, 40%). The purity of **4** was checked by HPLC analysis (System A, t_R=30.0 min see General methods). Compound **2** (10 mg, 0.021 mmol) was treated with a concentrated aqueous solution of NH_4OH (0.5 mL) in MeOH (0.5 mL) for 30 min at room temperature. The solvent was removed in vacuo and the crude was desalified by RP-HPLC (System D, t_R=18.8 min, see General methods) to give pure **3** (7.4 mg, 99%).

Compound **3**: white foam; $[\alpha]_D^{20}$ −15.6 (*c* 0.50, CH_3OH), ^{1}H NMR (400 MHz, CD_3OD) δ_H 7.89 (s, 1H, H-2), 7.87 (s, 1H, HC=N), 7.71 (s, 1H, HC=C), 5.82 (d, $J_{1',2'}$=4.8 Hz, 1H, H-1′), 4.44–4.41 (m, 1H, H-2′), 4.27–4.24 (m, 1H, H-3′), 4.02–3.99 (m, 1H, H-4′), 3.87 (s, 3H, CH_3OC=N), 3.82 (dd, $J_{5'a,5'b}$=12.1, $J_{5'a,4'}$=3.2 Hz, 1H, H_a-5′), 3.72 (dd, $J_{5'b,5'a}$=12.2, $J_{5'b,4'}$=3.8 Hz, 1H, H_b-5′), 3.63 (s, 3H, CH_3OC=O); ^{13}C NMR (100 MHz, CD_3OD) δ_C 171.4, 158.9, 150.4, 134.7, 133.1, 118.9, 92.7, 89.3, 85.7, 76.0, 71.2, 62.3, 53.9, 51.2; *m*/*z* (HRESIMS) 357.1421 ([M+H]$^+$, $C_{14}H_{21}N_4O_7$, requires 357.1410); IR (neat) ν_{max} 3330, 1634, 1575 cm^{-1}; UV (MeOH) λ_{max} 271 nm.

Compound **4**: oil; ^{1}H NMR (700 MHz, DMSO-d_6) δ_H (major tautomer) 8.90 (s, 1H, H-5), 8.77 (s, 1H, H-2), 6.34 (d, *J*=5.3 Hz, 1H, H-1′), 6.10–6.07 (m, 1H, H-2′), 5.68–5.63 (m, 1H, H-3′), 4.42–4.39 (complex signal, 2H, H-4′ and H_a-5′), 4.25 (dd, $J_{5'b,5'a}$=12.9, $J_{5'b,4'}$=6.0 Hz, 1H, H_b-5′), 4.20 and 4.19 (br s, 1H each, $H_{a,b}$-8), 3.63 (s, 3H, OCH_3), 2.12 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 1.99 (s, 3H, CH_3). ^{13}C NMR (175 MHz, CD_3OD) δ_C 169.9, 169.4, 169.2 (two carbons), 154.5, 151.9, 150.3, 145.4, 132.9, 85.9, 79.5, 71.8, 69.9, 62.6, 51.9, 38.0, 20.4, 20.3, 20.1; IR (neat) ν_{max} 1746, 1598, 1223 cm^{-1}; *m*/*z* (HRESIMS) 451.1451 ([M+H]$^+$, $C_{19}H_{23}N_4O_9$, requires 451.1465); UV (MeOH) λ_{max} 263 nm.

4.4. Reaction of 1b with 3-phenyl-2-propynenitrile. Synthesis of 5 and 6

A solution of **1b** (50 mg, 0.13 mmol) and 3-phenyl-2-propynenitrile (14 mg, 0.16 mmol), in dioxane (2.5 mL) was refluxed for 4 h (TLC monitoring, AcOEt/hexane, 8:2) and then the solvent was evaporated under reduced pressure. The crude was purified on a silica gel column eluted with increasing amounts of AcOEt in hexane (from 50 to 100%) to give **5** (30 mg, 45%) and **6** (19 mg, 30%), the purity of which was checked by HPLC analysis (System C, **5** t_R=22.3 min; **6** t_R=18.2 min, see General methods).

Compound **5**: white solid mp 116–117 °C; $[\alpha]_D^{20}$ −50.6 (*c* 0.11, CH_3OH), ^{1}H NMR (400 MHz, CD_3OD) δ_H 8.62 (s, 1H, H-2), 8.46 (s, 1H, H-8), 7.83–7.78 (m, 2H, Ph *ortho*-H), 7.54–7.50 (m, 1H, Ph *para*-H), 7.49–7.44 (m, 2H, Ph *meta*-H), 6.33 (d, $J_{1',2'}$=5.0 Hz, 1H, H-1′), 6.00–5.96 (m, 1H, H-2′), 5.69–5.66 (m, 1H, H-3′), 4.52–4.36 (complex signal, 3H, H-4′ and $H_{a,b}$-5′), 2.14 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.07 (s, 3H, CH_3); ^{13}C NMR (175 MHz, CD_3OD) δ_C 194.7, 172.2, 171.4, 171.2, 152.2, 149.1, 145.3, 143.5, 140.7, 132.3, 129.0, 125.1, 121.7, 88.4, 81.8, 74.6, 71.8, 64.1, 20.6, 20.5, 20.3; IR (neat) ν_{max} 2205, 1742, 1616, 1239 cm^{-1}; *m*/*z* (HRESIMS) 522.1620 ([M+H]$^+$, $C_{25}H_{24}N_5O_8$, requires 522.1625); UV (MeOH) λ_{max} 364 nm.

Compound **6**: oil; $[\alpha]_D^{20}$ −6.33 (c 0.6, CH_3OH), ^{1}H NMR (400 MHz, CD_3OD) δ_H 9.10 (s, 1H, H-2), 8.71 (s, 1H, H-8), 8.00–7.95 (m, 2H, Ph *ortho*-H), 7.73–7.67 (m, 1H, Ph *para*-H), 7.57–7.51 (m, 2H, Ph *meta*-H), 6.41 (d, $J_{1',2'}$=5.0 Hz, 1H, H-1′), 6.16–6.12 (m, 1H, H-2′), 5.78–5.75 (m, 1H, H-3′), 4.53–4.39 (complex signal, 3H, H-4′ and $H_{a,b}$-5′), 2.16 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.06 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ_C 192.8, 172.3, 171.4, 171.1, 154.7, 154.0, 152.9, 148.3, 136.6, 135.6, 133.4, 131.8, 129.6, 88.8, 81.8, 74.5, 71.9, 64.1, 20.9, 20.5, 20.4; IR (neat) ν_{max} 1747, 1674, 1582, 1226 cm^{-1}; *m*/*z* (HRESIMS) 483.1522 ([M+H]$^+$, $C_{23}H_{23}N_4O_8$, requires 483.1516); UV (MeOH) λ_{max} 265 nm.

4.5. Reaction of 1b with *N*-methylmaleimide. Synthesis of 7

A solution of **1b** (5 mg, 0.013 mmol) and *N*-methylmaleimide (14 mg, 0.13 mmol), in dioxane/toluene (1:1, v/v, 2.5 mL) was refluxed. After 5 h the process was complete (TLC monitoring, AcOEt/MeOH, 95:5) and the solvent was removed under reduced pressure. The crude was purified by HPLC (System B, t_R=16.0 min, see General methods) affording **7** (4.0 mg, 60%) as an inseparable mixture of diastereomers.

Compound **7**: oil; ^{1}H NMR (400 MHz, CD_3OD) δ_H (mixture of diastereomers) 8.95 (s, 0.3H), 8.64 (s, 0.3H), 8.23 (s, 0.7H), 8.09 (s, 0.7H), 6.36 (d, *J*=4.5 Hz, 0.3H), 6.19 (d, *J*=5.1 Hz, 0.7H), 6.15–6.11 (m, 1H, 0.3H), 5.98–5.92 (m, 0.7H), 5.80–5.73 (m, 0.3H), 5.69–5.62 (m, 0.7H), 5.29 (s, 0.7H), 5.16 (d, *J*=2.7 Hz, 0.3H), 4.51–4.32 (complex signal, 3H), 3.06 (s, 0.9H), 3.01 (s, 2.1H), 2.14 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.07 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ_C 177.4, 172.2, 171.3, 171.2, 153.7, 147.0, 146.2, 145.0, 141.4, 123.9, 89.0, 88.4, 88.2, 81.7, 74.6, 74.2, 73.9, 71.8, 69.1, 64.1, 25.4, 24.1, 20.7, 20.4, 20.3; IR (neat) ν_{max} 3335, 1740, 1699, 1584 cm^{-1}; *m*/*z* (HRESIMS) 506.1531 ([M+H]$^+$, $C_{21}H_{24}N_5O_{10}$, requires 506.1523); UV (MeOH) λ_{max} 267, 346 nm.

4.6. Preparation of 2′,3′,5′-tri-*O*-(*tert*-butyldimethylsilyl)-nebularine *N*1-oxide

2′,3′,5′-Tri-*O*-(*tert*-butyldimethylsilyl)-nebularine was prepared as described.[9b] A mixture of $MeReO_3$ (5 mg, 0.02 mmol) and 30% aqueous H_2O_2 (0.4 mL, 4.0 mmol) in methanol (6 mL) was stirred at room temperature for 10 min. Then 2′,3′,5′-tri-*O*-(*tert*-butyldimethylsilyl)-nebularine[9b] (595 mg, 1.0 mmol) in methanol (6 mL) was dropwise added while stirring. The stirring was continued at room temperature overnight. Then the solvent was removed under reduced pressure and the crude was purified on a silica gel column eluted with increasing amounts of AcOEt in hexane (up to 20%) to afford pure 2′,3′,5′-tri-*O*-(*tert*-butyldimethylsilyl)-nebularine *N*1-oxide **1c** (513 mg, 84% yield).

Compound **1c**: white solid, mp 126–127 °C; $[\alpha]_D^{20}$ −16.1 (*c* 0.80, $CHCl_3$), ^{1}H NMR (400 MHz, CD_3OD) δ_H 9.16 (br s, 1H), 9.02 (br s, 1H), 8.88 (s, 1H), 6.12 (d, *J*=4.7 Hz, 1H), 4.91–4.87 (m, 1H), 4.75–4.70 (m, 1H), 4.44–4.40 (m, 1H), 4.06 (dd, *J*=11.5, 4.1 Hz, 1H), 3.86 (dd, *J*=11.5, 2.4 Hz, 1H), 0.95 (br s, 18H), 0.82 (s, 9H), 0.15 (br s, 9H), 0.13 (s, 3H), 0.03 (s, 3H), −0.18 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ_C 150.0, 146.4, 145.6, 139.2, 135.2, 90.1, 87.0, 77.2, 72.9, 63.4, 26.5, 26.4, 26.2, 19.3, 18.9, 18.7, −4.0, −4.3, −4.7, −5.1, −5.3; *m*/*z* (HRESIMS) 633.3312 ([M+H]$^+$, $C_{28}H_{54}N_4NaO_5Si_3$, requires 633.3300); IR (neat) ν_{max} 2930, 2858, 1255, 1139, 837, 778 cm^{-1}; UV ($CHCl_3$) λ_{max} 280, 253 nm.

4.7. General procedure for reaction of 1c with Grignard reagents. Synthesis of 15–18

In a flamed round-bottomed flask charged with dry nitrogen, **1c** (50 mg, 0.082 mmol), dissolved in dry THF (0.5 mL), was added via cannula. To the flask the Grignard reagent (2 equiv) in THF was slowly added and the mixture was stirred for 2 h (TLC monitoring:

hexane/AcOEt, 4:6) at room temperature. The reaction was quenched by addition of a 1 M solution of NH_4Cl (1 mL), diluted with AcOEt (10 mL) and extracted with brine (1 mL). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated under rotary evaporation. The crude was dissolved in a mixture of Ac_2O–pyridine (6:4, 0.5 mL) and the solution was kept at 50 °C for 1 h. The crude was evaporated in vacuo and purified over a silica gel column eluted with increasing amounts of EtOAc in hexane (up to 20%). The fractions containing the product were collected and evaporated to afford pure **15**–**18**.

*4.7.1. 2′,3′,5′-Tri-O-(tert-butyldimethylsilyl)-6-methyl nebularine **15**.* Compound **15**: white solid (41 mg, 82% yield), $[\alpha]_D^{20}$ −36.8 (*c* 0.50, CH_3OH), mp 74–76 °C; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.83 (s, 1H, H-2), 8.38 (s, 1H, H-8), 6.11 (d, *J*=5.2 Hz, 1H, H-1′), 4.72–4.66 (m, 1H, H-2′), 4.34–4.32 (m, 1H, H-3′), 4.17–4.12 (m, 1H, H-4′), 4.02 (dd, *J*=11.4, 3.9 Hz, 1H, H-5_a′), 3.79 (dd, *J*=11.4, 2.5 Hz, 1H, H-5_b′), 2.87 (s, 3H, CH_3), 0.99 (s, 9H, $C(CH_3)_3$), 0.94 (s, 9H, $C(CH_3)_3$), 0.78 (s, 9H, $C(CH_3)_3$), 0.15 (s, 3H, CH_3), 0.14 (s, 3H, CH_3), 0.11 (br s, 6H, 2× CH_3), 0.05 (s, 3H, CH_3), −0.28 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 159.2, 152.2, 150.4, 142.7, 133.5, 88.2, 85.6, 75.8, 72.0, 62.5, 19.5, 18.5, 18.1, 17.8, −4.4, −4.6, −4.7, −5.1, −5.4; *m*/*z* (HRESIMS) 609.3679 ($[M+H]^+$, $C_{29}H_{57}N_4O_4Si_3$, requires 609.3688); IR (neat) ν_{max} 2955, 2930, 2859, 1599, 1256, 837, 777 cm^{-1}; UV ($CHCl_3$) λ_{max} 260 nm.

*4.7.2. 2′,3′,5′-Tri-O-(tert-butyldimethylsilyl)-6-vinyl nebularine **16**.* Compound **16**: colourless oil[22] (37 mg, 71% yield); $[\alpha]_D^{20}$ −44.6 (*c* 0.51, CH_3OH), ^1H NMR and ^{13}C NMR data are in agreement with reported data;[22] *m*/*z* (HRESIMS) 621.3681 ($[M+H]^+$, $C_{30}H_{57}N_4O_4Si_3$, requires 621.3688); IR (neat) ν_{max} 2931, 2859, 1583, 1256, 837, 778 cm^{-1}; UV ($CHCl_3$) λ_{max} 285 nm.

*4.7.3. 2′,3′,5′-Tri-O-(tert-butyldimethylsilyl)-6-phenyl nebularine **17**.* Compound **17**: colourless oil (45 mg, 82% yield); $[\alpha]_D^{20}$ −96.4 (*c* 0.11, CH_3OH) ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.01 (s, 1H, H-2), 8.82–8.75 (m, 2H, HPh), 8.46 (s, 1H, H-8), 7.61–7.49 (m, 3H, HPh), 6.18 (d, *J*=5.4 Hz, 1H, H-1′), 4.78–4.72 (m, 1H, H-2′), 4.38–4.32 (m, 1H, H-3′), 4.19–4.14 (m, 1H, H-4′), 4.05 (dd, *J*=11.3, 4.1 Hz, 1H, H-5_a′), 3.82 (dd, *J*=11.3, 2.8 Hz, 1H, H-5_b′), 0.97 (s, 9H, $C(CH_3)_3$), 0.96 (s, 9H, $C(CH_3)_3$), 0.79 (s, 9H, $C(CH_3)_3$), 0.16 (s, 3H, CH_3), 0.15 (s, 3H, CH_3), 0.13 (br s, 6H, 2× CH_3), 0.03 (s, 3H, CH_3), −0.25 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 154.9, 152.3, 143.3, 135.7, 131.6, 130.9, 129.8, 128.6, 88.2, 85.7, 75.7, 72.1, 62.6, 26.1, 25.8, 25.6, 18.5, 18.1, 17.8, −4.4, −4.6, −4.7, −5.0, −5.3, −5.4; *m*/*z* (HRESIMS) 693.3649 ($[M+Na]^+$, $C_{34}H_{58}N_4NaO_4Si_3$, requires 693.3664); IR (neat) ν_{max} 2954, 2930, 2858, 1579, 1567, 1256, 836, 777 cm^{-1}; UV ($CHCl_3$) λ_{max} 291 nm.

*4.7.4. 2′,3′,5′-Tri-O-(tert-butyldimethylsilyl)-6-propynyl nebularine **18**.* Compound **18**: colourless oil (41 mg, 80% yield); $[\alpha]_D^{20}$ −61.3 (*c* 0.12, CH_3OH) ^1H NMR (700 MHz, $CDCl_3$) δ_H 8.88 (s, 1H, H-2), 8.46 (s, 1H, H-8), 6.12 (d, *J*=5.2 Hz, 1H, H-1′), 4.66–4.62 (m, 1H, H-2′), 4.31–4.28 (m, 1H, H-3′), 4.16–4.13 (m, 1H, H-4′), 4.01 (dd, *J*=11.4, 3.9 Hz, 1H, H-5_a′), 3.80 (dd, *J*=11.4, 2.5 Hz, 1H, H-5_b′), 2.25 (s, 3H, CH_3), 0.95 (s, 9H, $C(CH_3)_3$), 0.93 (s, 9H, $C(CH_3)_3$), 0.77 (s, 9H, $C(CH_3)_3$), 0.15 (s, 3H, CH_3), 0.14 (s, 3H, CH_3), 0.10 (br s, 6H, 2× CH_3), 0.05 (s, 3H, CH_3), −0.29 (s, 3H, CH_3); ^{13}C NMR (175 MHz, $CDCl_3$) δ_C 152.5, 151.2, 143.9, 142.2, 134.7, 97.1, 88.1, 85.8, 76.0, 75.3, 72.0, 62.5, 26.0, 25.8, 25.6, 18.5, 18.0, 17.8, 5.1, −4.4, −4.6, −4.7, −5.1, −5.3; *m*/*z* (HRESIMS) 655.3519 ($[M+Na]^+$, $C_{31}H_{56}N_4NaO_4Si_3$, requires 655.3507); IR (neat) ν_{max} 2956, 2859, 2243, 1580, 1259, 837, 776 cm^{-1}; UV ($CHCl_3$) λ_{max} 286 nm.

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