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Dual-Participation Protecting Group Solves the Anomeric Stereocontrol Problems in Glycosylation Reactions

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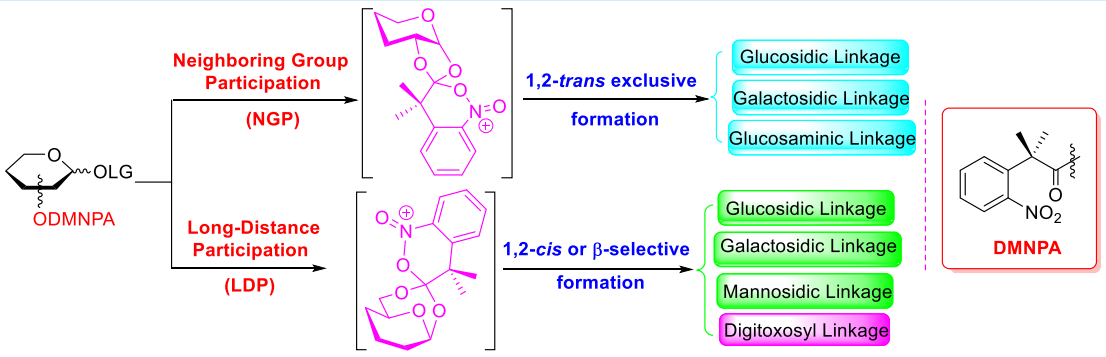
Supporting Information



ABSTRACT: The 2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl (DMNPA) group permits, via robust neighboring group participation (NGP) or long distance participation (LDP) effects, the stereocontrolled 1,2-*trans*, 1,2-*cis*, as well as *β*-2,6-dideoxy glycosidic bond generation, while suppressing the undesired orthoester byproduct formation. The robust stereocontrol capability of the DMNPA is due to the dual-participation effect from both the ester functionality and the nitro group, verified by control reactions and DFT calculations and further corroborated by X-ray spectroscopy.

It has been proven that the unique chemical structure bestows the 2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl (DMNPA) group with a rapid deprotection process and the broad mutual orthogonality to the generally applied protecting groups (PGs) in carbohydrate chemistry.[1] The rapid deprotection of the DMNPA group topples the long-lasting notion that the steric PGs inevitably suffer from sluggish/difficult deprotection,[2] while the broad mutual orthogonality of the DMNPA group to other PGs improves the efficiency of glycosides, especially complex glycoside synthesis both by saving the steps of PG manipulations and by enhancing the efficiency thereof.[3] Further analysis of the chemical structure of the DMNPA group reveals that the *ortho*-positioned nitro group might be exploited as the second participating group[4] to enforce the directing effects, the neighboring group participation (NGP) effect,[5] and the long distance participation (LDP) effect,[6] of the ester functionality of DMNPA (Figure 1). The participation of the nitro group requires a close proximity between the nitro group and the ester carbonyl functionality, which can be created by the *gem*-dimethyl group through the Thorpe−Ingold effect.[7] Leveraging on the intensified directing effects of the DMNPA group, theoretically, the tough and chronic stereocontrol problem of glycosylation reactions could be reduced to the regioselective

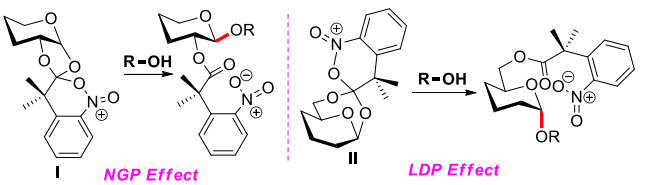


Figure 1. Stereoselective glycosylation by NGP and LDP effects of the DMNPA group.

installation of the DMNPA group (for NGP effect: C2-hydroxy group acylation, for LDP effect: hydroxy groups except for C2-OH acylation). Through systematic investigations, the robust stereocontrol capability of the DMNPA group was established, leading to the stereoselective construction of 1,2-*trans*, 1,2-*cis*, as well as the *β*-2,6-dideoxy glycosidic linkages. Furthermore, the proposed dual-participation mechanism was determined, not only by control reactions and DFT calculations but also by X-ray spectroscopy, for the first time.

With the continuous emergence of cases where 2-*O*-acylated donors afford compromised 1,2-*trans* stereoselectivity, ester-

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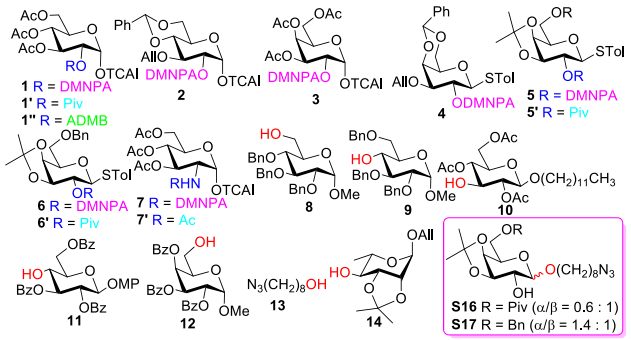
type PGs with reliable NGP effect are highly desirable.[8] The NGP effect of DMNPA was first evaluated with glucosyl trichloroacetimidate[9] (TCAI) donor **1**, and under the effect of catalytic amounts of TMSOTf, the couplings with acceptors **8** and **9** proceeded stereoselectively to afford **15** and **16** (97% and 93% yields, respectively; Table 1, entries 1 and 2). With **10** as the acceptor, which was shown to give nonstereoselectivity when reacted with the perbenzoylated glucosyl TCAI donor,[10] the condensations with **1** and **2** proceeded β-stereoselectively to afford **17** and **18** under the identical conditions (82% and 97% yields, entries 3 and 6). As a comparison, replacing the DMNPA group of **1** with pivaloyl (Piv)[11] (**1′**) and 4-acetoxy-2,2-dimethylbutanoyl (ADMB)[12] (**1″**) groups, the two PGs widely applied to a secure reliable NGP effect, led to an evident drop in stereoselectivity (**17′** α/β = 1:10 and **17″** α/β = 1:3.6, entries 4 and 5).

Table 1. Stereocontrol Capability of the DMNPA Group via the NGP Effect



entry	donor	acceptor	conditions	results[a,b]
1	**1**	**8**	TMSOTf (0.1 equiv), CH_2Cl_2, 4A MS, 0 °C to rt	**15** (97%, only β)
2	**1**	**9**	TMSOTf (0.1 equiv), CH_2Cl_2, 4A MS, 0 °C to rt	**16** (93%, only β)
3	**1**	**10**	TMSOTf (0.1 equiv), CH_2Cl_2, 4A MS, 0 °C to rt	**17** (82%, only β)
4	**1′**	**10**	TMSOTf (0.1 equiv), CH_2Cl_2, 4A MS, 0 °C to rt	**17′** (81%, α/β = 1:10)
5	**1″**	**10**	TMSOTf (0.1 equiv), CH_2Cl_2, 4A MS, 0 °C to rt	**17″** (74%, α/β = 1:3.6)
6	**2**	**10**	TMSOTf (0.1 equiv), CH_2Cl_2, 4A MS, 0 °C to rt	**18** (97%, only β)
7	**3**	**11**	TMSOTf (0.2 equiv), CH_2Cl_2, 4A MS, −25 °C	**19** (70%, only β)
8	**4**	**12**	NIS (1.5 equiv), TMSOTf (0.2 equiv), DCM 5A MS, −25 °C	**20** (72%, only β)
9	**4**	**9**	NIS (1.5 equiv), TMSOTf (0.2 equiv), DCM 5A MS, −25 °C	**21** (94%, only β)
10	**5**	**13**	NIS (1.4 equiv), TfOH (0.25 equiv), DCM 4A MS, 0 °C	**22** (89%, only β)
11	**5′**	**13**	NIS (1.4 equiv), TfOH (0.25 equiv), DCM 4A MS, 0 °C	**22′** (51%) + **S16** (24%)
12	**6**	**13**	NIS (1.4 equiv), TfOH (0.25 equiv), 4A MS, 0 °C	**23** (83%, only β)
13	**6′**	**13**	NIS (1.4 equiv), TfOH (0.25 equiv), 4A MS, 0 °C	**23′** (69%) + **S17** (26%)
14	**7**	**8**	TMSOTf (0.2 equiv), CH_2Cl_2, 5A MS, 0 °C to rt	**24** (86%, only β)
15	**7′**	**8**	TMSOTf (0.2 equiv), CH_2Cl_2, 5A MS, 0 °C to rt	**24′** (90%)
16	**7**	**14**	TMSOTf (0.2 equiv), CH_2Cl_2, 5A MS, 0 °C to rt	**25** (94%, only β)

[a]Isolated yield. [b]The α/β ratios were determined by separation of the α/β anomers with silica gel chromatography.

Selective construction of β-galactosidic linkages is problematic due to the presence of the C4 axial hydroxy group, whose stabilizing effect on the oxocarbenium intermediate of the galactosyl donor favors the formation of α-galactoside even for donors equipped with 2-*O*-acyl NGP groups.[13] In addition, the PGs on the galactosyl donor have profound effects on the outcome of galactosylation. For example, the 4,6-*O*-benzylidene acetal[14] as well as the 3,4-*O*-isopropylidene ketal[15] can magnify the α-glycosylation bias of galactosyl donors, leading to the further compromised β-stereoselectivity of galactosylations. However, with the DMNPA as the C2-OH PG, the glycosylations between **3** and **11**,[13] **4** and **7**/**8**,[13] as well as **5**/**6** and **13**[16] proceed β-stereoselectively to furnish **19**, **20**, **21**, **22**, and **23** efficiently under the conditions identical to those reported in the literature (above 70% yields), regardless of the protection pattern of galactosyl donors (entries 7−10 and 12). In contrast, with Piv as the PG of C2-OH, donors **5′** and **6′**, when coupled with **13**, provided **22′** and **23′** in only 51% and 69% yields, respectively. The main byproducts were determined to be Piv-migrated compounds, which were isolated with 24% (for **S16**) and 26% (for **S17**) yields as mixtures of α/β anomers (entries 11 and 13).[17]

The feasibility of DMNPA as a PG for C2-NH_2 of glucosamine was examined by condensations between **7** and **8**/**14**, which provided disaccharides **24** and **25** successfully (86% and 94% yields, entries 14 and 16). Strikingly, when **7′** was subjected to condensation with **8**, only the oxazoline product **24′** was detected (entry 15).[18]

It is worth mentioning that with DMNPA as the C2-OH PG no orthoester formation was observed in all above glycosylations, while with DMNPA as the C2-NH_2 PG, the formation of the oxazoline intermediate was observed; however, it could be activated *in situ* to further react with acceptors.[19]

Inspired by the impressive NGP effect, the LDP effect of the DMNPA group was subsequently evaluated, which has been proven subtle and highly substrate sensitive (Table 2).[20] Glucosyl TCAI donors **26** and **27** with DMNPAs attached at C6-OHs gave good to excellent α-stereoselectivity when coupled with acceptors **8** and **9** (**32**−**35**, over 90% yields and above 10:1 α/β ratios, entries 1−4). Similarly, DMNPAs located at C-3 and C-4 OHs of galactosyl TCAI donors **28** and **29** steered the galactosylations with **8** and **9** α-selectively, providing **36**−**39** (above 5:1 α/β ratios and over 63% yields, entries 5−8). Furthermore, the LDP effect of DMNPA could even be exploited in the construction of the challenging β mannosidic and digitoxosidic linkages. Thus, with **8** as an acceptor, the mannosyl TCAI donor **30** bearing a C4-*O*-DMNPA afforded mannoside **40** with a good β-stereoselectivity (α/β = 1:8.2, entry 9), while the digitoxosyl ABz[21] donor **31** with the DMNPA group installed at C3-OH glycosylated **8** and **9** β-selectively to furnish **41** and **42** (over 80% yield and above 5:1 β/α ratios, entries 11 and 14). Striking comparisons were offered with the mannosyl TCAI donor **30′** and digitosoxosyl ABz donors **31′** and **31″**, which uniformly provided more inferior β-stereoselectivity in comparison to the corresponding DMNPA donors under the identical conditions (entries 12, 13, and 15), although either

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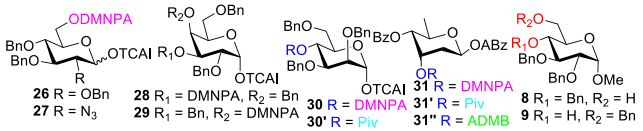
Table 2. Stereocontrol Effect of the DMNPA Group via the LDP Effect



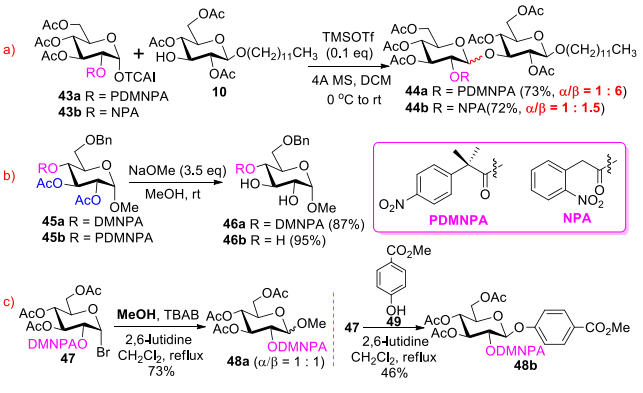
entry	donor	acceptor	conditions	results[a]
1	**26**	**8**	TMSOTf (0.1 equiv), CH_2Cl_2, 4A MS, 0 °C to rt	**32** (91%, only α)
2	**27**	**8**	TMSOTf (0.1 equiv), CH_2Cl_2, 4A MS, −40 °C	**33** (91%, α/β = 13:1)
3	**26**	**9**	TMSOTf (0.1 equiv), CH_2Cl_2, 4A MS, −40 °C	**34** (92%, α/β = 14:1)
4	**27**	**9**	TMSOTf (0.1 equiv), CH_2Cl_2, 4A MS, −40 °C	**35** (93%, α/β = 10:1)
5	**28**	**8**	TMSOTf (0.1 equiv), CH_2Cl_2, 4A MS, 0 °C to rt	**36** (86%, α/β = 5.3:1)
6	**29**	**8**	TMSOTf (0.1 equiv), CH_2Cl_2, 4A MS, 0 °C to rt	**37** (94%, α only)
7	**28**	**9**	TMSOTf (0.1 equiv), CH_2Cl_2, 4A MS, −40 °C	**38** (63%, α only)
8	**29**	**9**	TMSOTf (0.1 equiv), CH_2Cl_2, 4A MS, −40 °C	**39** (70%, α only)
9	**30**	**8**	TMSOTf (0.1 equiv), CH_2Cl_2, 4A MS, −78 °C	**40** (94%, α/β = 1:8.2)
10	**30′**	**8**	TMSOTf (0.1 equiv), CH_2Cl_2, 4A MS, −78 °C	**40′** (87% α/β = 1:3)
11	**31**	**8**	$Ph_3PAuOTf$ (0.2 equiv), CH_2Cl_2, 4A MS, rt	**41** (86%, β only)
12	**31′**	**8**	$Ph_3PAuOTf$ (0.2 equiv), CH_2Cl_2, 4A MS, rt	**41′** (98%, α/β = 1:1.5)
13	**31″**	**8**	$Ph_3PAuOTf$ (0.2 equiv), CH_2Cl_2, 4A MS, rt	**41″** (75%, α/β = 1:1.8)
14	**31**	**9**	$Ph_3PAuOTf$ (0.2 equiv), CH_2Cl_2, 4A MS, rt	**42** (83%, α/β = 1:5)
15	**31′**	**9**	$Ph_3PAuOTf$ (0.2 equiv), CH_2Cl_2, 4A MS, rt	**42′** (80%, α/β = 1:2.1)

[a]Isolated yields. [b]The α/β ratios were determined by separation of the α/β anomers with silica gel chromatography.

the Piv groups or the ADMB groups were incorporated in the donors (β/α ratio around 2:1).

The efficient NGP as well as LDP effects of the DMNPA group intrigued us to decipher the underlying mechanism. As the NGP and LDP effects of Piv and ADMB groups are less effective than those of the DMNPA group, the steric hindrance of DMNPA should not be responsible for its reliable stereocontrol capability. To elucidate the indispensable structural elements for DMNPA to exercise an efficient stereocontrolling effect, donors **43a,b** bearing C2-OH-attached 2,2-dimethyl-2-(*para*-nitrophenyl)acetyl (PDMNPA) and (2-nitrophenyl)acetyl (NPA)[22] groups were synthesized and subjected to condensation with **10** (Scheme 1a). The evident drop in stereoselectivity for **44a** (α/β = 1:6) and **44b** (α/β = 1:1.5) indicates that the position of the nitro group (*ortho* vs *para*) and the *gem*-dimethyl group is decisive for the stereodirecting effect of the DMNPA group. The reactivity divergence between DMNPA (**45a**) and PDMNPA (**45b**) groups, with the former being inert to **46a** and the latter being sensitive to harsh basic conditions (**46b**), further highlights the importance of the position of the nitro group (Scheme 1b). The capability in suppressing orthoester formation was then evaluated with bromide **47** (Scheme 1c). Surprisingly, no matter whether methanol or *p*-(methoxycarbonyl)phenol (**49**) was selected as the acceptor, not even trace amounts of

Scheme 1. Control Reactions



orthoesters were detected.[23] Instead, only the glycosylation products **48a,b** were isolated.

The necessary structural elements of the *ortho*-nitro and *gem*-dimethyl groups for efficient stereocontrol exert the base-inert property as well as the efficient inhibition of orthoester formation, implying that a certain kind of interaction between the nitro and ester carbonyl group exists, which is supported by the Thorpe−Ingold effect of the *gem*-dimethyl group. The interaction attenuates the electrophilicity of the ester carbonyl group, resulting in the exceptional stability of DMNPA to basic conditions; meanwhile, the interaction can evolve into a dual-participation effect[24] during glycosylation to guarantee the high stereoselectivity via the nitro-enforced ester participation. In addition to the enhanced participating effect of the ester functionality, the orthoester formation can also be efficiently prohibited by the dual participation, further improving the stereoselectivity especially when the NGP effect is exploited to steer the anomeric chirality, as transient orthoester formation has been determined as the mechanism responsible for the compromised 1,2-*trans* stereoselectivity for the donor with C2-OH NGP PGs.[9,25] The X-ray diffraction structures of compounds **1** and **S35** (Figure 2) strongly supported the proposed dual-participation mechanism, as the distance between the oxygen atom of the nitro group and the carbonyl carbon atom was measured to be 2.5−2.8 Å shorter than the sum of the van der Waals radii of C and O atoms (3.22 Å).[26]

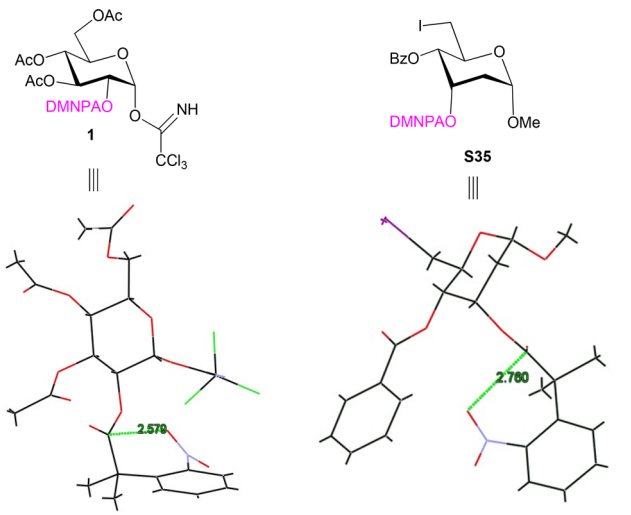


Figure 2. X-ray structures of DMNPA containing compounds **1** and **S35**.

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To further corroborate the dual-participation mechanism, several possible reactive intermediates were investigated by a computational approach.[27] DFT calculations, using the B3LYP hybrid functional and 6-311G(d,p) as the basis set in combination with a polarizable continuum model (PCM) using CH_2Cl_2 as solvent, revealed that **I**, in which the 2-*O*-DMNPA nitro functionality stabilizes the dioxolenium ion, is 7.5 kcal/mol more stable than the dioxolenium ion **I′** lacking this interaction (Figure 3A). Similarly, dual participation of the

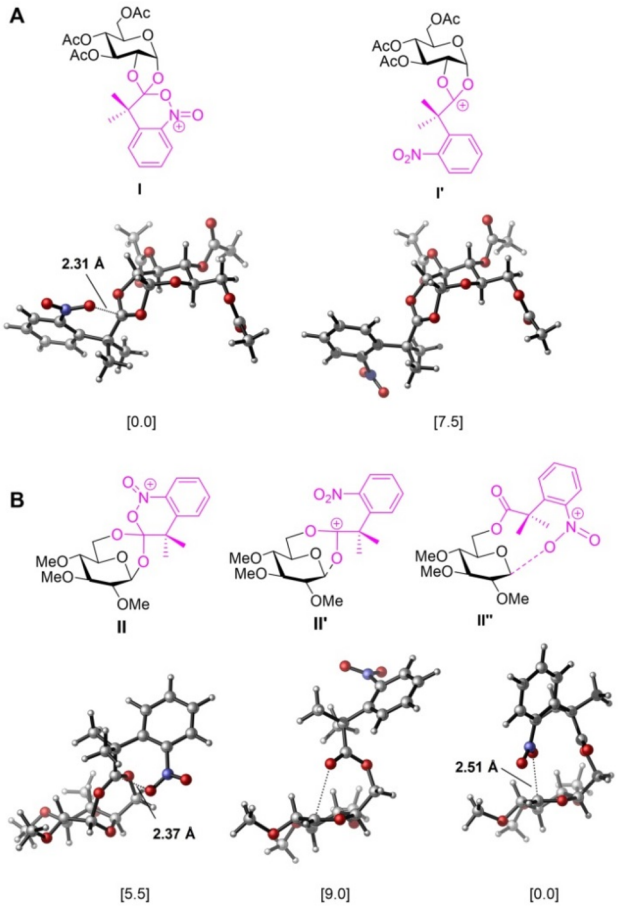

Figure 3. PCM(CH_2Cl_2)-B3LYP/6-311G(d,p)-optimized geometries of found relevant reactive intermediates for donors **1** (A) and **26** (B). The corresponding solvated Gibbs free energy in kcal·mol^{-1} is denoted in brackets.

6-*O*-DMNPA ester provided species **II**, which is 3.5 kcal/mol more stable than the dioxolenium ion **II′** formed by the attack of the 6-*O*-ester to the anomeric center without the nitro participation. Notably, our calculations indicated that the lowest energy intermediate that could be formed was intermediate **II″**, in which the nitro functionality of the DMNPA group directly stabilizes the $^4H_3$-oxocarbenium ion (Figure 3B), proving another participating manner of the nitro group. The LDP effect of the 3-*O*-DMNPA ester was probed by the digitoxose system, revealing that the dual participation by the nitro group provides 7.0 kcal/mol of stabilization to the dioxolenium ion.[27] Overall, the calculations strongly support the stabilization of the formed dioxolenium ions by the appended nitro functionality.

In summary, with DMNPA as the chirality-controlling group, either through the NGP effect or through the LDP effect, the highly stereoselective construction of 1,2-*trans*, 1,2-*cis*, as well as *β*-digitoxosyl glycosidic linkages has been achieved while eliminating the drawbacks of orthoester formation inherent to conventional ester-type PGs. The stereoselectivity is much higher than that provided by Piv and ADMB groups, which have been introduced to secure high stereoselectivity. Through systematic control reactions and DFT calculations, a dual-participation mechanism was disclosed for the first time, which was further corroborated by X-ray spectroscopy. In combination with the mutually orthogonal property of the deprotection process,[1] the reliable stereocontrol capability of the DMNPA group could simplify the chronic chirality control problem of glycosylation reaction to regioselective DMNPA group installation. Thus, it will find broad applications in the synthesis of bioactive glycosides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03321.

Detailed experimental procedures, characterization, and copies of ^{1}H and ^{13}C NMR spectra of new compounds (PDF)

Accession Codes

CCDC 1868958−1868959 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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