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Chemistry of 2-Nitroglycals: A One-Pot Three-Component Stereoselective Approach toward 2-*C*-Branched *O*-Galactosides

Pavan K. Kancharla and Yashwant D. Vankar*

Department of Chemistry, Indian Institute of Technology, Kanpur 208 016, India

vankar@iitk.ac.in

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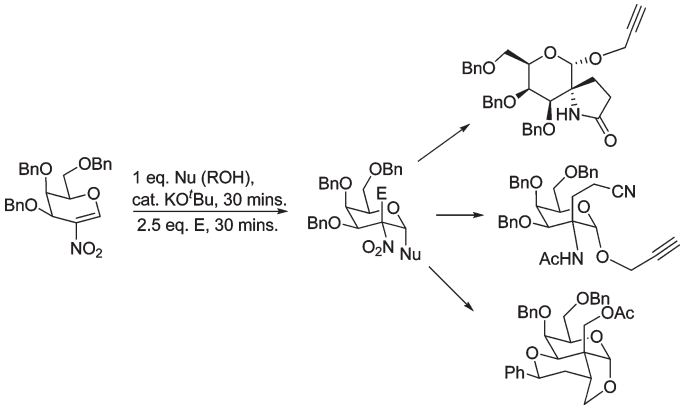

A convenient one-pot three-component approach for the synthesis of 2-*C*-branched *O*-glycosides has been developed from 2-nitroglycals. These 2-*C*-branched sugars have been shown to be precursors for a variety of biologically and synthetically relevant molecules.

Introduction

2-Nitroglycals are versatile intermediates for the stereoselective synthesis of various glycosides.[1] Besides being good Michael acceptors, they also permit (2 + 3) and (2 + 4) cycloadditions, thus permitting the preparation of a number of other useful carbohydrate derived synthons. Optimized conditions have been developed for the stereoselective addition of a variety of nucleophiles to the 2-nitroglycals, resulting in the synthesis of several *O*-glycosides,[2] thioglycosides,[3] glycophosphonates,[4] *C*-glycosides,[5] and *N*-glycosides (for the synthesis of nucleosides).[6] Further, the nitro functionality is of enormous importance in organic synthesis, particularly as it can readily be converted into an amino or a hydroxylamino[7] group. Also, the nitro groups allow the generation of a reactive radical in the presence of *n*-Bu_3SnH-AIBN[8] that could be exploited further. As a result, 2-nitroglycals serve as useful intermediates in the synthesis of 2-deoxy-2-amino glycosides, which are constituents of several nucleoside and aminoglycosidic antibiotics.[9] The base-catalyzed 2-nitroglycal concatenation is extensively studied and has also been applied in the synthesis of mucins,[10a] a family of highly *O*-glycosylated glycoproteins that play an important role in various biological processes.[10b,c]

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Although C-glycosides can be readily prepared[11] from glycals, their derivatives, and other monosaccharides, C-functionalization at centers other than the anomeric carbon is still a challenge for chemists. Since C-branched sugars are abundant in nature and many antibiotics[12] and natural products[13] contain these branched sugars as structural subunits, several approaches toward them have been reported in the literature.[14] Further, some methods of introducing a carbon chain at *C*-2 require multisteps,[15] while others involve the use of toxic reagents such as mercury and tin[16] or moisture-sensitive organolithium and Grignard reagents.[17] However, notable contribution has been made by Linker and coworkers[18] in the synthesis of 2-*C*-branched sugars through ceric ammonium nitrate mediated addition of active methylenes to glycals that were extended to the synthesis of glycoaminoacids,[19] glycoacetic acids,[20] and glycosamines.[21] The other effective ways of entering into 2-*C*-branched sugars include the usage of 1,2-cyclopropanated sugars and related systems[22] and many others.[23]

Our group has been actively involved in the chemistry of nitro sugars in general[24] and 2-nitroglycals in particular en route to the development of novel glycosidase inhibitors[5,25] and in the synthesis of 2-deoxy-2-amino *C*-glycosides.[5a] In view of the above-mentioned developments in the synthesis of 2-*C*-branched sugars and our interest in developing the chemistry of nitrosugars, we were prompted to use 2-nitroglycals as synthons for the synthesis of 2-*C*-branched sugars. Since α,*β*-unsaturated nitro compounds are known to undergo intramolecular Michael−Michael[26] and Michael−Henry aldol[27] cascade in a two-component reaction, we anticipated the utility of 2-nitroglycals in a one-pot three-component approach to attain the 2-*C*-branched glycosides. One-pot reactions,[28] being practically single-step reactions, are easier to handle than stepwise synthesis. Our approach toward the synthesis of 2-*C*-branched *O*-glycosides also allows further functionalization due to the presence of the nitro group.

Results and Discussion

Schmidt et al. have reported that *O*-nucleophiles, for stereoelectronic reasons, selectively add[1a] from the α-side to 2-nitrogalactals in the presence of a strong base, generating a nitronate ion intermediate.[1,2b] This nitronate ion after protonation from the *β*-side provides the 2-deoxy-2-nitro-α-galactosides. Our aim was to trap the nitronate ion intermediate with a suitable carbon electrophile to generate the 2-*C*-branched glycosides. For this purpose, in our initial attempt we have added 1 equiv of acrylonitrile to a stirring reaction mixture of 2-nitrogalactal **1** (Table 1) and benzyl alcohol in the presence of a catalytic amount of KO^{t}Bu in THF for 2 h. To our delight, we observed the formation of a clean new product as gauged by thin layer chromatographic analysis; however, the reaction could not proceed further to completion even after several hours. Optimization of the reaction conditions led us to use 2.5 equiv of acrylonitrile at 25 °C under the same conditions, which led to a clean reaction. Further, out of the four possible isomers that can result as a result of the generation of two new stereocenters, the one-pot Michael−Michael reaction on 2-nitrogalactal led to the exclusive formation of a single diastereomer **3** of 2-nitro-2-*C*-branched glycoside in 75% yield. The scope of the reaction was explored by using different alcohols as Michael donors and methyl acrylate as well as acrylonitrile as the second Michael acceptors, and our results are summarized in Table 1.

The stereochemical outcome of the Michael−Michael addition was proved unambiguously by the X-ray crystal structure[29] obtained for compound **4** (see Supporting Information) wherein the two new groups added at C-2, i.e., the propargyl group and the -CH_2CH_2COOMe, were found to be placed in a 1,2-diaxial fashion. Further, the stereochemistry was also assigned through COSY and NOE analysis of the acetamido derivative **31**, vide infra, derived from the nitro compound **5** (see Supporting Information). The generation of the stereocenter at the anomeric position is in consonance with the results reported by Schmidt et al.,

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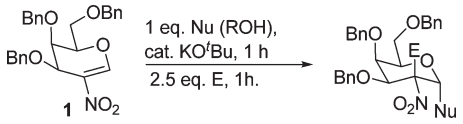
(29) CCDC number for the crystal data of the compound **4**: 789893. We thank Mr. Ashutosh Kumar Mishra for solving the crystal structure of the compound.

TABLE 1. One-Pot Michael−Michael Reaction with 2-Nitrogalactal



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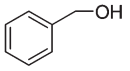
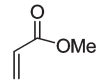
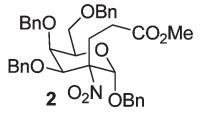
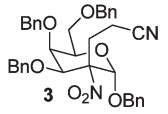
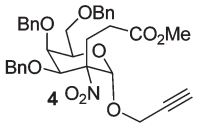
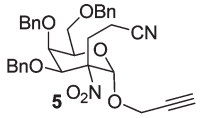
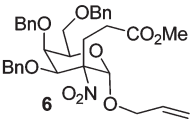
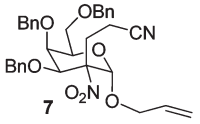
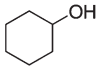
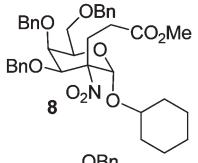
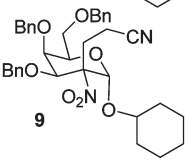
1		a) 	 **2**	82%
		b) 	 **3**	75%
2		a	 **4**	81%
		b	 **5**	81%
3		a	 **6**	77%
		b	 **7**	74%
4		a	 **8**	65%
		b	 **9**	63%

i.e., the nucleophilic attack occurs at the anomeric center from the α-side, whereas the second stereocenter generated at the *C*-2 carbon results according to the transition state depicted in Figure 1.

The nitronate ion generated at the *C*-2 center, during the electrophile trapping, orients itself in the conformation **11** rather than **12** due to the possible unfavorable 1,3-diaxial interaction between the *C*-4-*O*-benzyl group and the nitro group, thus allowing the electrophilic attack from *β*-side.

We also subjected the 2-nitrogalactal to one-pot Michael−Henry aldol reaction (Table 2) with paraformaldehyde as an electrophile with the same set of alcohols as initial Michael donors. Although the yields of the products **13**−**17** were moderate in comparison to the Michael−Michael reaction,

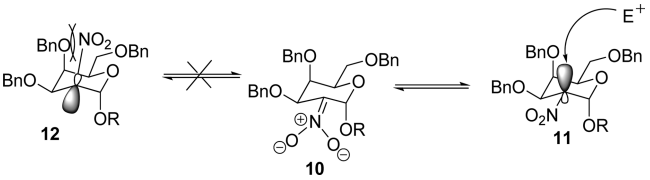
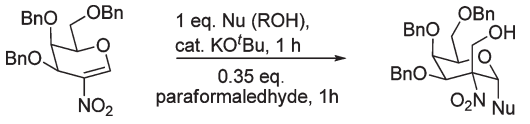
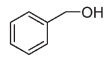
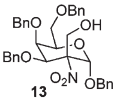
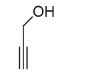
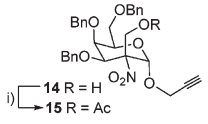
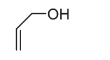
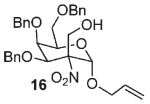
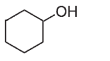
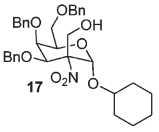


FIGURE 1. Transition states to depict the stereochemical outcome of the products.

we again observed the exclusive formation of the diaxially substituted Michael−Henry aldol adducts in all of the cases as confirmed on the basis of COSY and NOE studies. Thus, for example, during NOE spectral studies of compound **16** (Figure 2), irradiation of the signal for H-2 at *δ* 5.06 showed

TABLE 2. One-Pot Michael−Henry Addition with 2-Nitrogalactal



Entry	Nu (Nucleophile)	Product	Yield
1		 **13**	72%
2		 i) **14** R = H → **15** R = Ac	65%[a]
3		 **16**	67%
4		 **17**	61%

(i) Et_3N, Ac_2O

[a]Overall yield for 2 steps.

no enhancement in the signals for H-4 and H-6 that appeared at δ 4.78 and 4.12, respectively, suggesting the axial orientation of the allyloxy group, but showed enhancement in the signal for one of the methylenic protons of the -CH_2OH group. Besides, irradiation of those methylenic protons did not result in any enhancement of the signal for H-4, indicating the axial orientation of the -CH_2OH group.

The above-described method has also been applied on 2-nitroglucal **18** for the generation of the corresponding *gluco* derivatives of 2-*C*-branched-2-nitro-*O*-glycosides. The reactions were performed using acrylonitrile, methyl acrylate, and paraformaldehyde as the electrophiles. The yields and the diastereoselectivity were found to be poor, as expected, due to the poor stereoselectivity of the first Michael addition.[30] Unlike 2-nitrogalactal, addition of the electrophile in this case took place from the equatorial side and the nitro group was axially oriented, suggesting the absence of or reduced 1,3-diaxial repulsions in the intermediate, thus forming thermodynamically stable products rather than kinetically controlled products. However, trace amounts of the other two diastereomers were also observed in all of the cases (**21**, **24**, **30**) (Table 3) whose structures could not be established due to the difficulty in procuring them in pure forms. The stereochemical outcome of both diastereomers was confirmed through NOE analysis (Figure 2) of compounds. Thus, for example, irradiation of the signal for H-2 of the major diastereomer **19** at δ 5.14 did not result in the enhancement of the signals for either H-4 or H-6 protons appearing at δ 3.85−3.89. On the other hand, in the other diastereomer **20**, irradiation of the signal for H-2 at δ 4.80 led to the enhancement of H-4 and H-6 protons at δ 3.67 and

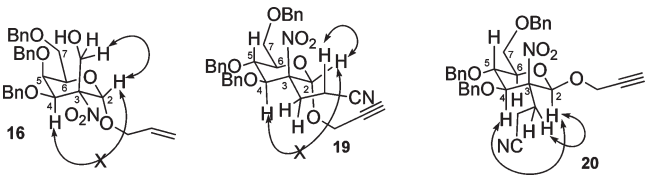


FIGURE 2. Diagnostic NOE correlations observed for the compounds **16**, **19**, and **20**.

3.53, respectively, suggesting the axial and equatorial orientation of the propargyl group, respectively. Besides, irradiation of H-5 proton at δ 4.74 and at 4.54 in either cases, i.e., compounds **19** and **20**, respectively, did not result in the enhancement of protons of the side chain at *C*-2 indicating the equatorial orientation of the -CH_2CH_2CN group (Figure 2).

Synthesis of 2-*C*-Branched Amino Sugar, Amino Acid, and Spirolactam. 2-Amino-2-deoxy-*O*-glycosides are constituents of several nucleoside and aminoglycosidic anitibiotics,[31] and the abundance of 2-*N*-acetamidosugars,[32] *N*-acetylglucosamine and *N*-acetylgalactosamine in glycoproteins, proteoglycans, and glycolipids makes them attractive targets for metabolic engineering. The recent study of metabolic cell surface engineering with the artificial *C*-2-carbon isosters[33] shows the need of more number of such analogues. In the present study, the above-described Michael−Michael and Michael−Henry aldol adducts have been shown to be the precursors for the synthesis of some novel 2-*C*-branched-2-amino *O*-glycosides by successfully reducing the nitro group of the compound **5** to amino group by using Zn/HCl/AcOH and subsequently protecting as *N*-acetate **31** (Scheme 1).

Compound **4** was also subjected to these conditions followed by treatment with triethylamine, which resulted in an interesting sugar-derived C_2-spiro-γ-lactam **32** (Scheme 2). However, by subjecting the crude amino product to an excess of acetic anhydride in the presence of triethylamine led to the γ-amino butyric acid (GABA) derivative **33**, thus providing an elegant entry into biologically important sugar amino acids[34] (SAA). Absence of the methyl singlet at δ 3.52 in the ^{1}H NMR spectrum and appearance of a strong absorption at 1670 cm^{-1} in FT-IR spectrum for the compound **32**, as well as appearance of a methyl singlet at δ 1.7 in the ^{1}H NMR spectrum and absorption at 1695 cm^{-1} in FT-IR spectrum of compound **33** along with other spectroscopical evidence, confirmed the formation of the spirolactam **32** and the sugar amino acid derivative **33** ,respectively.

Radical Cyclization of 2-*C*-Branched 2-Nitrosugars. The nitro functionality was further exploited to show the utility of these adducts by treating them with *n*-Bu_3SnH in the presence of AIBN. Tertiary nitro containing molecules being excellent substrates for radical reactions helped us to develop a simple route for the generation of two C−C bonds at the C-2 position of the sugar molecules starting from 2-nitroglycals, which otherwise may require many steps. Although bicyclic sugars are reported in the literature through radical

(30) Khodair, A. I.; Pachamuthu, K.; Schmidt, R. R. *Synthesis* **2004**, *1*, 53.

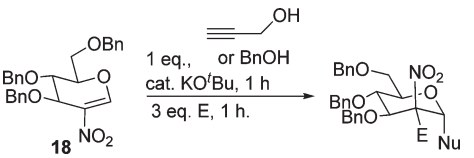
(31) *Glycochemistry Principles, Synthesis, and Applications*; Wang, P. G., Bertozzi, C. R., Eds.; Marcel Dekker, Inc.: New York, 2001.

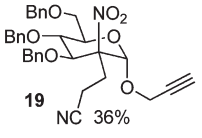
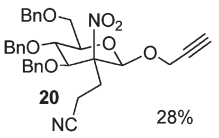
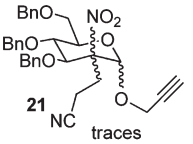
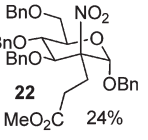
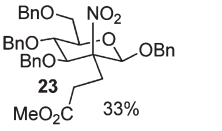
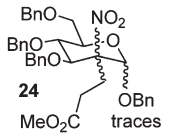
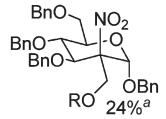
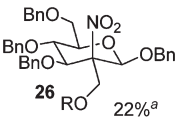
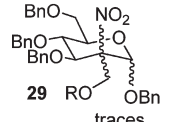
(32) Zheng, Z.; Cummings, R. D.; Pummill, P. E.; Kincade, P. W. *J. Clin. Invest*. **1997**, *100*, 1217.

(33) Hang, H. C.; Bertozzi, C. R. *J. Am. Chem. Soc*. **2001**, *123*, 1242.

(34) Gruner, S. A. W.; Locardi, E.; Lohof, E.; Kessler, H. *Chem. Rev*. **2002**, *102*, 491.

TABLE 3. One-Pot Michael−Michael and Michael−Henry Addition with 2-Nitroglucal

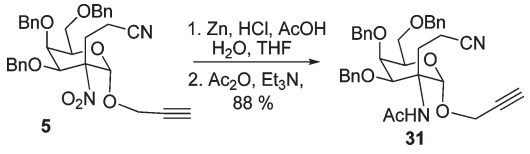


Entry	E (Electrophile)	Product		
1		 **19** NC 36%	 **20** NC 28%	 **21** NC traces
2		 **22** MeO_2C 24%	 **23** MeO_2C 33%	 **24** OBn MeO_2C traces
3	paraformaldehyde	 **25** R = H, **26** R = Ac (i) 24%[a]	 **27** R = H, **28** R = Ac (i) 22%[a]	 **29** R = H, **30** R = Ac (i) traces

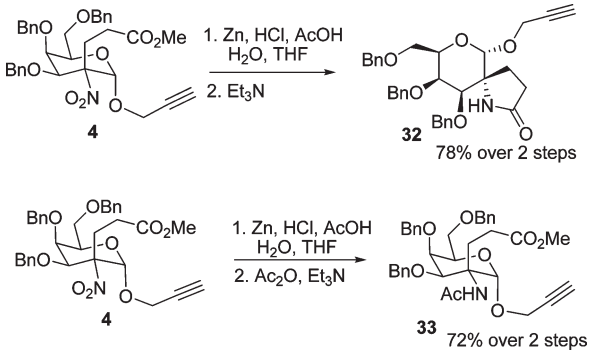
(i) Et_3N, Ac_2O

[a]Overall yield for 2 steps.

SCHEME 1. Synthesis of 2-*C*-Branched *N*-Acetyl Galactosamine Derivative



SCHEME 2. Synthesis of C_2-Spiro-γ-lactam and Synthesis of *C*-Glycosylated GABA Derivative



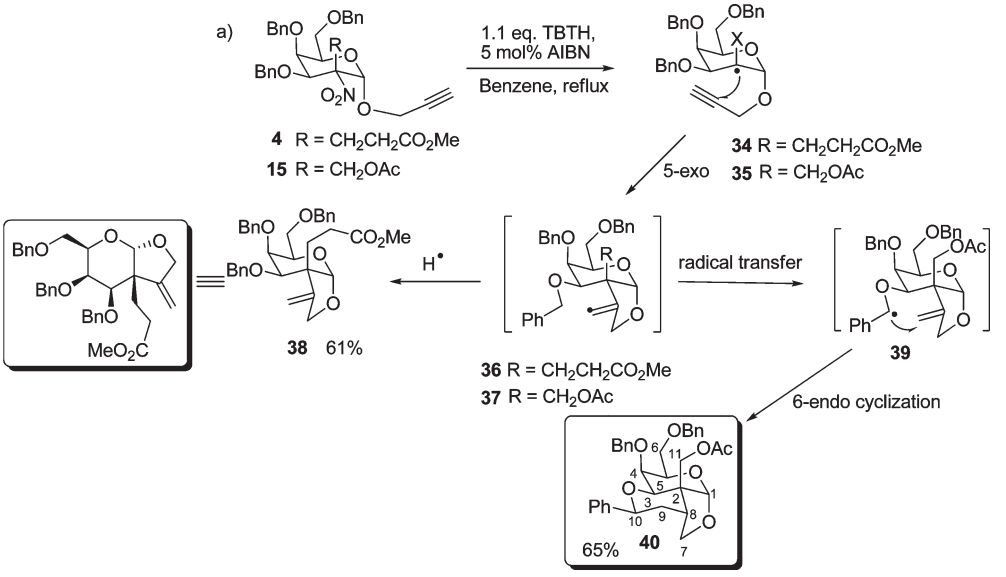
cyclizations,[35] the present study appears to be the first one to show the radical chemistry of 2-nitrosugars and also to synthesize bicyclic sugars with a quaternary center at the C-2 position.

When compound **4** was treated with 1.1 equiv of *n*-Bu_3SnH and 2 mol % of AIBN, the tertiary radical generated at C-2 trapped the triple bond of the tethered propargyl group intramolecularly, to yield a bicyclic sugar **38** (Scheme 3). Interestingly, when the same reaction was performed on compound **15**, the cyclization process did not stop at the bicyclic stage and a further 6-*endo* cyclization was observed in tandem after the radical transfer from vinyl to a more stable *O*-benzylic postion in the proximity, resulting in a complex tricyclic molecule **40** (Scheme 3). It is likely that the radical **36** picks up a hydrogen atom α to the ester moiety from -CH_2COOMe via a six-membered transition state in an intramolecular fashion resulting in a stabilized electrophilic radical that is then reduced by *n*-Bu_3SnH leading to **38**. In contrast, radical **37** prefers to form a more stabilized radical **39** resulting in the tricycle **40,** rather than forming a radical α to the −OAc group. Cyclization to form **40** had occurred stereospecifically resulting in a single diastereomer, although two new stereocenters were generated. The structure of this intriguing skeleton was unambiguously assigned using all the spectral data including COSY, DEPT-135, and NOE analysis (Figure 3).

The appearance of two protons below δ 2.0 and another proton at δ 2.81 in the ^{1}H NMR spectrum of compound **40** indicated the saturation of the exocyclic double bond formed after the initial cyclization. Extensive and careful analysis of the COSY and DEPT-135 spectra revealed that the intermediate compound **37** with an exocyclic double bond underwent a further cyclization to form a tricycle (Scheme 3).

(35) (a) Yanada, R.; Koh, Y.; Nishimori, N.; Matsumura, A.; Obika, S.; Mitsuya, H.; Fujii, N.; Takemoto, Y. *J. Org. Chem.* **2004**, *69*, 2417. (b) Yamazaki, O.; Yamaguchi, K.; Yokoyama, M.; Togo, H. *J. Org. Chem.* **2000**, *65*, 5440.

SCHEME 3. Radical Chemistry of 2-*C*-Branched 2-Nitrosugars



Further, irradiation of the signal for proton H-8 at δ 2.81 resulted in the enhancement of the signal for the protons H-1, H-7, and H-9 at δ 5.36, 4.15, and 1.90, respectively. Further, irradiation of the signal for proton H-3 at δ 3.98 showed enhancement in the signals for the protons corresponding to H-5 as well as H-10 at δ 4.25 and 4.81, respectively, indicating a *cis*-1,3-diaxial relation between the protons H-3 and H-10. This data confirmed the absolute stereochemistry at the two new stereocenters generated (Figure 3).

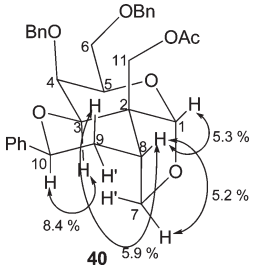
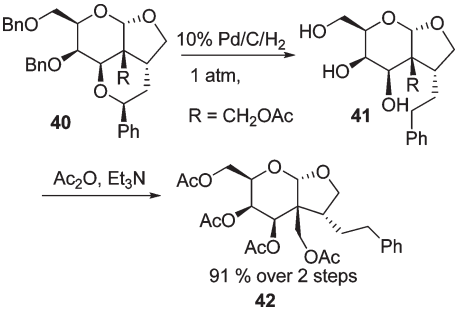


FIGURE 3. Diagnostic NOE correlations observed for the tricyclic compound **40**.

Further, despite the possibility of both 5-*exo* and 6-*endo* cyclizations, the steric constraints of the double bond perhaps allows the cyclization to take place in the 6-*endo* mode. As a further synthetic proof for the formation of tricyclic molecule, compound **40** was subjected to hydrogenolysis to get a bicyclic sugar, and the crude free hydroxyl derivative was acetylated using excess acetic anhydride in the presence of triethylamine to obtain a tetraacetate **42**. Its ^{1}H NMR spectrum showed the presence of phenyl protons above δ 7.0 along with the four methyl peaks δ 2.0 corresponding to four acetate groups, indicating the transfer of the benzyl group from C-3 position to C-9 during the hydrogenolysi,s which is possible only if the precursor was a tricycle (Scheme 4). Thus, we obtained a stereochemically complex tricyclic structure in two steps from 2-nitrogalactal with four new stereocenters generated in a stereoselective fashion. Interestingly, the tricyclic core structure of the compound **40** has been found to be the subunit of natural products striatin C,[36] which is highly active against a variety of Gram-positive bacteria and has been isolated from the basidiomycete *Cyathus striatus*, and also erinacine J,[37] which was isolated from *Hericium erinaceum*.

SCHEME 4. Synthetic Evidence for the Formation of the Tricyclic Molecule



Conclusion

In summary, we have developed a simple one-pot three-component approach toward the synthesis of 2-*C*-branched 2-nitro-*O*-glycosides. The utility of the method has been shown by exploring the functionalities of the Michael−Michael and Michael−Henry aldol products toward synthesizing biologically relevant 2-*C*-branched galactosamine, a sugar amino acid derivative, and a sugar-based spirolactam. The adducts were also utilized in radical cyclizations to generate bicyclic sugar as well as generating a stereochemically intriguing tricyclic molecule.

Experimental Section

General Procedure for the One-Pot Michael−Michael Addition Reactions. To a stirred solution of 2-nitroglycal (100 mg, 0.21 mmol) and an alcohol (0.22 mmol) in THF (1 mL) was

(36) Hecht, H.-J. *J. Chem. Soc., Chem. Commun.* **1978**, 665.
(37) Kawagishi, H.; Masui, A.; Tokuyama, s.; Nakamura, T. *Tetrahedron* **2006**, *62*, 8463.

added dropwise a solution of potassium *tert*-butoxide (1 mL, 10 mg/mL) in THF at 0 °C. The reaction mixture was brought to room temperature and stirred for 1 h, after which methyl acrylate/acrylonitrile (0.52 mmol) was added. After stirring the reaction mixture for an additional 1 h, it was then neutralized with Amberlite IRA resin (H^+ form). The resin was filtered off, and the solvent was evaporated to get the crude product. Purification of the residue by column chromatography yielded the Michael−Michael adducts.

General Procedure for the One-Pot Michael−Henry aldol Addition Reactions. To a stirred solution of 2-nitroglycal (100 mg, 0.21 mmol) and an alcohol (0.22 mmol) in THF (1 mL) was slowly added a solution of potassium *tert*-butoxide (1 mL, 10 mg/mL) in THF at 0 °C. After complete addition, the reaction mixture was brought to room temperature. After the reaction mixture stirred for 1 h, paraformaldehyde (0.22 mmol) was added. After completion of the reaction, the mixture was neutralized with Amberlite IRA resin (H^+ form). The resin was filtered off, and the solvent was evaporated to get the crude product. Purification of the residue by column chromatography yielded the Michael−Henry aldol adducts.

General Procedure for Acetylation Reactions. The compound (50 mg) was taken up in a mixture of acetic anhydride and triethylamine (1:1, 1 mL) and stirred for 1 h. Volatiles were evaporated in rotary evaporator and the residue was purified through column chromatography to yield the acetylated products.

Methyl-3-((2*S*,3*R*,4*R*,5*R*,6*R*)-2,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-3-nitrotetrahydro-2*H*-pyran-3-yl)propanoate (2). Yield 82%; R_f: 0.35 (hexane/ethyl acetate, 9:1), $[\alpha]^{28}_D$ = +50.0 (*c* 0.3, CH_2Cl_2). IR (neat) ν_{max}: 3064, 3031, 2921, 2854, 1736, 1591, 1548, 1453, 1261, 1094, 1045, 737, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.36−7.15 (m, 20H, Ar−H), 4.98 (s, 1H), 4.84 (d, *J* = 10.7 Hz, 1H), 4.80 (d, *J* = 9.5 Hz, 1H), 4.75−4.64 (m, 2H), 4.54−4.42 (m, 4H), 4.07 (m, 2H), 3.63 (m, 1H), 3.54 (m, 1H), 3.50 (s, 3H), 3.50 (s, 1H), 3.07 (m, 1H), 2.90 (m, 1H), 2.87 (m, 1H), 2.21 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 140.8, 137.9, 137.7, 137.5, 135.9, 128.4−126.9 (m, Ar−C), 100.6, 91.8, 75.5, 73.8, 73.5, 73.3, 70.2, 69.6, 68.4, 65.3, 51.3, 29.9, 29.6. HRMS calcd for $C_{38}H_{42}NO_9$ $[M + H]^+$ 656.2860, found 656.2866.

3-((2*S*,3*R*,4*R*,5*R*,6*R*)-2,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)-3-nitrotetrahydro-2*H*-pyran-3-yl)propanenitrile (3). Yield: 75%; R_f: 0.32 (hexane/ethyl acetate, 9:1), $[\alpha]^{28}_D$ = +73.3 (*c* 0.3, CH_2Cl_2). IR (neat) ν_{max}: 3030, 2922, 2852, 2248, 1607, 1549, 1495, 1456, 1352, 734, 696 cm^{-1}. ^1H NMR (400 MHz, CDCl3): δ 7.31−7.07 (m, 20H, Ar−H), 4.83 (s, 1H), 4.72 (d, *J* = 10.2 Hz, 1H), 4.65−4.61 (m, 2H), 4.61 (d, *J* = 12.6 Hz, 1H), 4.50−4.37 (m, 4H), 4.01−4.00 (d, *J* = 4.4 Hz, 2H), 3.62−3.60 (t, J = 6.3 Hz, 1H), 3.57 (dd, *J* = 7.3 Hz, *J* = 4.4 Hz, 1H) 3.47 (dd, *J* = 5.8 Hz, *J* = 9.2 Hz, 1H), 3.03 (m, 1H), 2.75 (m, 1H), 2.55 (t, *J* = 6.3 Hz, 1H), 2.12 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.9, 137.6, 137.5, 137.1, 135.7, 128.7−127.0 (m, Ar−C), 119.0, 100.2, 91.2, 76.0, 73.8, 73.7, 73.6, 70.5, 69.7, 30.9, 13.8. HRMS calcd for $C_{37}H_{39}N_2O_7$ $[M + H]^+$ 623.2757, found 623.2752.

Methyl-3-((2*S*,3*R*,4*R*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-(benzyloxymethyl)-3-nitro-2-(prop-2-ynyloxy)tetrahydro-2*H*-pyran-3-yl)propanoate (4). Yield: 81%; R_f: 0.32 (hexane/ethyl acetate, 9:1), $[\alpha]^{28}_D$ = +55.0 (*c* 0.8, CH_2Cl_2). IR (neat) ν_{max}; 3060, 3032, 2924, 2853, 2120, 1733, 1548, 1450, 1373, 743, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34−7.16 (m, 15H, Ar−H), 5.11 (s, 1H), 4.85 (d, *J* = 10.7 Hz, 1H), 4.78 (d, *J* = 10.7 Hz, 1H), 4.74 (d, *J* = 10.5 Hz, 1H), 4.65 (d, *J* = 3.2 Hz, 1H), 4.51−4.43 (m, 3H), 4.19 (d, *J* = 2.4 Hz, 2H), 4.08−4.05 (m, 2H), 3.63 (t, *J* = 9.5 Hz, 1H) 3.57 (dd, *J* = 6.8 Hz, *J* = 9.4 Hz, 1H), 3.52 (s, 3H), 3.07 (m, 1H), 2.92 (m, 1H), 2.65 (m, 1H), 2.41 (m, 1H), 2.20 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 137.9, 137.8, 137.7, 128.4−127.6 (m, Ar−C), 100.2, 91.6, 75.6, 73.8, 73.6, 73.4, 69.9, 68.1, 55.5, 51.3, 30.0, 29.9. HRMS calcd for $C_{34}H_{38}NO_9$ $[M + H]^+$ 604.2547, found 604.2545.

3-((2*S*,3*R*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-nitro-2-(prop-2-ynyloxy)tetrahydro-2*H*-pyran-3-yl)propanenitrile (5). Yield: 81%; R_f: 0.40 (hexane/ethyl acetate, 4:1), $[\alpha]^{28}_D$ = +64.2 (*c* 0.95, CH_2Cl_2). IR (neat) ν_{max}: 3064, 3032, 2923, 2856, 2251, 2122, 1602, 1554, 1496, 1453, 1354, 740, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37−7.16 (m, 15H, Ar−H), 5.05 (s, 1H, H-2), 4.80 (d, *J* = 10.2 Hz, 1H), 4.71−4.67 (m, 3H, 2 −OC*H*Ph, H-4), 4.54−4.47 (m, 3H, 3 −OC*H*Ph), 4.19 (d, *J* = 2.4 Hz, 2H, $-OCH_2C{\equiv}CH$), 4.10−4.05 (m, 2H, H-5, H-6), 3.64 (t, *J* = 9.0 Hz, 1H, H-7) 3.57 (dd, *J* = 5.8 Hz, *J* = 9.2 Hz, 1H, H-7′), 3.12 (m, 1H), 2.81 (m, 1H), 2.64 (t, *J* = 6.3 Hz, 1H), 2.44 (t, *J* = 2.4 Hz, 1H), 2.20 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 137.0, 128.5−127.6 (m, Ar−C), 118.7, 99.5, 90.9, 76.0, 73.7, 73.6, 69.9, 67.8, 55.6, 30.8, 13.7. HRMS calcd for $C_{33}H_{35}N_2O_7$ $[M + H]^+$ 571.2444, found 571.2448.

Methyl-3-((2*S*,3*R*,4*R*,5*R*,6*R*)-2-(allyloxy)-4,5-bis(benzyloxy)-6-(benzyloxymethyl)-3-nitrotetrahydro-2*H*-pyran-3-yl)propanoate (6). Yield: 77%; R_f: 0.60 (hexane/ethyl acetate, 4:1), $[\alpha]^{28}_D$ = +41.4 (*c* 0.84, CH_2Cl_2). IR (neat) ν_{max}: 3030, 2923, 2869, 1736, 1548, 1452, 1095, 1057, 737, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34−7.16 (m, 15H, Ar−H), 5.77 (m, 1H, $-OCH_2$-C*H*=CH_2), 5.24−5.17 (m, 2H, $-OCH_2CH{=}CH_2$), 4.95 (s, 1H, H-2), 4.85 (d, *J* = 10.7 Hz, 1H), 4.78 (d, *J* = 10.9 Hz, 1H), 4.74 (d, *J* = 10.7 Hz, 1H), 4.68 (d, *J* = 2.9 Hz, 1H, H-4), 4.53−4.43 (m, 3H), 4.14−4.05 (m, 3H, $-OCHH'CH{=}CH_2$, H-5, H-6), 3.96 (d, *J* = 6.3 Hz, *J* = 12.9 Hz, 1H, $OCHH'CH{=}CH_2$), 3.66−3.55 (m, 2H, H-7, H-7′), 3.51 (s, 3H), 3.07 (m, 1H) 2.92 (m, 1H), 2.60 (m, 1H), 2.22 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 137.9, 137.7, 137.5, 132.5, 129.3−127.5 (m, Ar−C), 118.3, 100.4, 91.8, 75.6, 75.5, 73.8, 73.5, 73.3, 69.4, 69.4, 69.0, 68.4, 51.3, 29.9, 29.9. HRMS calcd for $C_{34}H_{40}NO_9$ $[M + H]^+$ 606.2703, found 606.2706.

((2*S*,3*R*,4*R*,5*R*,6*R*)-2-(Allyloxy)-4,5-bis(benzyloxy)-6-(benzyloxymethyl)-3-nitrotetrahydro-2*H*-pyran-3-yl)methanol (16). Yield: 67%; R_f: 0.52 (hexane/ethyl acetate, 4:1), $[\alpha]^{28}_D$ = +22.6 (*c* 3.5, CH_2Cl_2). IR (neat) ν_{max}: 3502, 3029, 2919, 1640, 1548, 1494, 1339, 1081, 1040, 734, 694 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.37−7.18 (m, 15H, Ar−H), 5.80 (m, 2H), 5.06 (s, 1H, H-5), 4.87 (d, *J* = 10.3 Hz, 1H), 4.81 (d, *J* = 2.3 Hz, 1H, H-5), 4.78 (d, *J* = 4.9 Hz, 1H, H-4), 4.75 (d, *J* = 10.3 Hz, 1H), 4.72 (dd, *J* = 2.7 Hz, *J* = 12.2 Hz, 1H, $-CHOH$), 4.70 (m, 1H), 4.53 (d, *J* = 11.8 Hz, 1H), 4.50 (d, *J* = 11.1 Hz, 1H), 4.44 (d, *J* = 11.8 Hz, 1H), 4.31 (t, *J* = 12.2 Hz, 1H), 4.13 − 4.07 (m, 2H, H-6, allylic −C*H*), 3.97 (dd, *J* = 6.1 Hz, *J* = 12.6 Hz, 1H, allylic −C*H*′), 3.65 (dd, *J* = 7.6 Hz, *J* = 9.1 Hz, 1H, H-7), 3.57 (dd, *J* = 6.1 Hz, *J* = 9.1 Hz, 1H, H-7′), 3.30 (dd, *J* = 2.7 Hz, *J* = 11.1 Hz, 1H, −O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.7, 136.9, 132.5, 128.7−127.7 (m, Ar−C), 127.0, 118.6, 97.4, 92.1, 75.9, 73.9, 73.8, 73.7, 69.2, 68.9, 68.2, 65.4, 65.4. HRMS calcd for $C_{31}H_{36}NO_8$ $[M + H]^+$ 550.2441, found 550.2443.

Preparation of Compounds 19 and 20. 2-Nitroglucal was subjected to the general procedure with propargyl alcohol as the Michael donor and acrylonitrile as the Michael acceptor to obtain the crude product, which was purified by column chromatography to give compounds **19** and **20**.

3-((2*S*,3*R*,4*R*,5*S*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-nitro-2-(prop-2-ynyloxy)tetrahydro-2*H*-pyran-3-yl)propanenitrile (19). Yield: 36%; R_f: 0.55 (hexane/ethyl acetate, 4:1), $[\alpha]^{28}_D$ = −44.0 (*c* 0.35, CH_2Cl_2). IR (neat) ν_{max}: 3063, 3031, 2924, 2868, 2249, 2121, 1553, 1496, 1362, 1108, 1058, 1026, 738, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.36−7.14 (m, 15H, Ar−H), 5.12 (s, 1H, H-2), 4.99 (d, *J* = 10.2 Hz, 1H), 4.91 (d, *J* = 10.2 Hz, 1H), 4.81 (d, *J* = 10.7 Hz, 1H), 4.74 (t, *J* = 4.6 Hz, 1H, H-5), 4.66 (d, *J* = 12.2 Hz, 1H), 4.51 (m, 2H), 4.21 (d, *J* = 2.4 Hz, 1H), 3.88 (m, 2H, H-4, H-6), 3.77 (dd, *J* = 1.7 Hz, *J* = 12.9 Hz, 1H, H-7), 3.65 (br, d, *J* = 10.7 Hz, 1H, H-7′), 2.94 (m, 1H), 2.64−2.48 (m, 2H), 2.47 (d, *J* = 2.4 Hz, 1H), 2.25 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.6, 137.5, 137.3, 128.5−127.6 (m, Ar−C), 118.6, 99.1, 91.4, 79.4, 76.4, 76.0, 75.3,

73.6, 72.0, 67.4, 60.3, 55.5, 29.6. 13.5. HRMS calcd for $C_{33}H_{35}N_2O_7$ $[M + H]^+$ 571.2444, found 571.2449.

3-((2*R*,3*S*,4*R*,5*S*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-nitro-2-(prop-2-ynyloxy)tetrahydro-2*H*-pyran-3-yl)propanenitrile (20). Yield: 28%; R_f: 0.31 (hexane/ethyl acetate, 4:1), $[\alpha]^{28}{}_D = -17.7$ (*c* 0.45, CH_2Cl_2). IR (neat) ν_{max}: 3061, 3028, 2920, 2851, 2249, 2120, 1553, 1453, 1363, 1116, 1082, 1021, 739, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38−7.16 (m, 15H, Ar−H), 4.98 (d, J = 11.4 Hz, 1H), 4.80 (s, 1H, H-2), 4.74−4.57 (m, 5H), 4.54 (d, J = 4.4, 1H, H-5), 4.38 (m, 2H), 3.86−3.79 (m, 2H, H-7, H-7′), 3.67 (d, J = 8.5 Hz, 1H, H-4), 3.53 (d, J = 9.7, 2.2 Hz, 1H, H-6), 2.65−2.54 (m, 2H), 2.52 (m, 1H), 2.48 (m, 1H), 2.09 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.7, 137.4, 136.7, 128.8−127.9 (m, Ar−C), 119.1, 96.8, 91.6, 81.4, 76.5, 75.8, 75.5, 74.8, 73.7, 68.3, 55.7, 29.6, 13.0. HRMS calcd for $C_{33}H_{35}N_2O_7$ $[M + H]^+$ 571.2444, found 571.2447.

***N*-((2*S*,3*R*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-(2-cyanoethyl)-2-(prop-2-ynyl-oxy)tetrahydro-2*H*-pyran-3-yl)-acetamide (31).** Compound **5** (60 mg) was dissolved in a mixture of THF (7 mL), concentrated HCl (0.3 mL), acetic acid (1.6 mL), and H_2O (3.0 mL) and cooled to 0 °C. Zn dust (135 mg, 20 equiv) was added to it portion-wise. After 1 h of stirring at 0 °C, the residue was filtered, and the reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with water, saturated aqueous $NaHCO_3$, and water, and dried over anhydrous Na_2SO_4. After evaporation of the solvents the crude amine was dissolved in 0.5 mL of acetic anhydride and 0.5 mL of triethylamine and was stirred for 0.5 h. Removal of volatiles under reduced pressure followed by purification on silica gel afforded the corresponding *N*-acetyl galactosamine (53 mg) in 88% yield. R_f: 0.65 (hexane/ethyl acetate, 7:3), $[\alpha]^{28}{}_D = -29.8$ (*c* 0.5, CH_2Cl_2). IR (neat) ν_{max}: 3407, 3288, 3029, 2920, 2852, 2248, 2120, 1674, 1452, 1365, 1097, 1043, 738, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 1H, NH), 7.37−7.22 (m, 15H, Ar−H), 4.84 (s, 1H, H-2), 4.79 (d, J = 11.2 Hz, 1H), 4.60−4.43 (m, 5H), 4.21 (m, 2H), 3.94 (m, 1H, H-5), 3.90 (t, J = 7.0 Hz, 1H, H-6), 3.68 (d, J = 3.1 Hz, 1H, H-4), 3.63 (dd, J = 9.2, 7.3 Hz, 1H, H-7), 3.56 (dd, J = 9.0, 5.8 Hz, 1H, H-7′), 2.94−2.83 (m, 2H), 2.73 (m, 1H), 2.39 (t, J = 2.2 Hz, 1H, acetylinic), 2.10 (m, 1H) 2.00 (s, 3H, NHAc). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 137.9, 137.7, 137.5, 128.5−127.5 (m, Ar−C), 120.9, 97.9, 78.9,78.1, 75.7, 75.0, 74.2, 73.6, 73.4, 69.6, 68.5, 63.2, 54.4, 27.9, 12.7. HRMS calcd for $C_{35}H_{38}KN_2O_6$ $[M + K]^+$ 621.2367, found 621.2367.

Methyl-3-((3a*R*,4*R*,5*R*,6*R*,7a*S*)-4,5-bis(benzyloxy)-6-(benzyloxymethyl)-3-methylenehexahydro-2*H*-furo[2,3-*b*]pyran-3a-yl)propanoate (38). To a solution of compound **4** (110 mg) in benzene were added *n*-Bu_3SnH (0.47 mL, 1.77 mmol) and AIBN (19 mg), and the mixture was refluxed for 5 h. After monitoring the disappearance of the starting material by TLC analysis, the volatiles were removed, and the residue was purified by column chromatography to obtain the bicyclic sugar **38** (65 mg) in 64% yield. R_f: 0.35 (hexane/ethyl acetate, 4:1), $[\alpha]^{28}{}_D = +40.0$ (*c* 0.1, CH_2Cl_2). IR (neat) ν_{max}: 3087, 3063, 2954, 2854, 1739, 1454, 1369, 1235, 1028, 736, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34−7.26 (m, 15H, Ar−H), 5.14 (s, 1H, H-7a), 5.00 (m, 2H, H-8, H-8′), 4.81 (d, J = 11.4 Hz, OC*H*Ph), 4.79 (d, J = 11.2 Hz, OC*H*Ph), 4.58 (m, 5H, 4(OC*H*Ph), H-2), 4.33 (m, 1H, H-2′), 4.23 (m, 1H, H-5), 3.96 (t, J= 2.6 Hz, 1H, H-4), 3.71(m, 2H, H-6, H-6′), 3.60 (s, 3H, COOC*H*$_3$), 3.53 (d, J = 2.6 Hz, 1H, H-3), 2.35 (m, 2H, H-10, H-10′), 2.26 (m, 2H, H-9, H-9′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0, 148.5, 138.0, 137.9, 128.3−127.4 (m, Ar−C), 106.8, 102.9, 79.1, 73.7, 73.4, 72.3, 71.8, 68.8, 68.3, 50.4, 29.0, 28.9, 22.8. HRMS calcd for $C_{34}H_{39}O_7$ $[M + H]^+$ 559.2696, found 559.2699.

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Supporting Information Available: Details on general experimental methods; copies of ^1H NMR and ^{13}C NMR spectra of all the new compounds, COSY and NOE spectra of compounds **5**, **6**, **16**, **19**, **20**, **31**, and **40**; DEPT-135 spectrum of compound **40**; and the crystallographic details of compound **4** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.