

HETEROCYCLES, Vol. 98, No. 4, 2019, pp. 544 - 550. © 2019 The Japan Institute of Heterocyclic Chemistry
Received, 23rd January, 2019, Accepted, 5th March, 2019, Published online, 28th March, 2019
DOI: 10.3987/COM-19-14044

SYNTHESIS OF *N*-ALKYL SUBSTITUTED AZASUGAR-TETRAZOLE HYBRID MOLECULES VIA UGI-AZIDE REACTION

Hairong Luo,* Bangjian Xu, Lingyu Zhang, and Meihang Chen

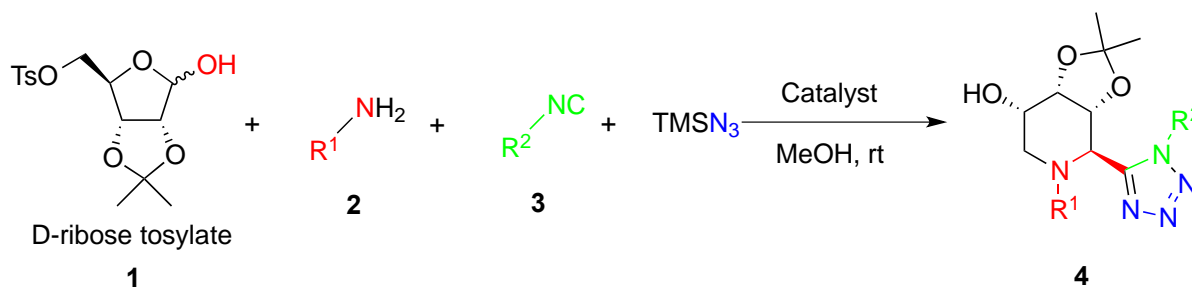
College of Material and Chemical Engineering, Tongren University, Tongren 554300, China. E-mail: luohair@163.com

Abstract – An effective and facile method for the synthesis of *N*-alkyl substituted azasugar-tetrazole hybrid molecules is described. The one-pot Ugi-azide reaction provides convenient access to synthesis of α -tetrazolyl azasugar scaffolds as potential glucosidase inhibitors in moderate to good yields in methanol catalyzed by Lewis acid under mild conditions.

Azasugar derivatives, which are a family of carbohydrate mimetics, have attracted considerable attention due to their intriguing biological properties.¹ Their broad spectrum of activity is evidenced by their use as tumor metastasis,² diabetes,³ viral infections and lysosomal storage disorders.⁴ Two azasugars have been approved as drugs: GlysetTM and ZavescaTM, for the treatment of noninsulin-dependent diabetes⁵ and Gaucher's disease,⁶ respectively. The structure diversity of azasugar has widened their scope towards the inhibition of various carbohydrate processing enzymes. These interesting biological activities have inspired many efforts in the synthesis of azasugars and their derivatives.⁷ Cheng reported an efficient preparation of 2-heterocyclyl polyhydroxylated pyrrolidines and biological testing showed that subtle structural variations have drastic effects on the inhibitory activities against glucosidases.⁸ Inspired by a large number of biomolecules containing a five-membered heterocycle, we are curious whether we can develop a new 2-tetrazolyl azasugar skeleton and increase the molecular diversity.

Based on our literature search, we selected the Ugi-azide synthesis of tetrazoles from primary amines.⁹ The Ugi-azide reaction, that TMSN₃ modified Ugi involves condensation of an appropriately substituted aldehyde with amine, has led to the generation of unique cyclic scaffolds such as ketopiperazine-tetrazoles, azepine-tetrazoles, benzodiazepine-tetrazoles, and quinoxaline-tetrazoles.¹⁰ To the best of our knowledge, however, there is no report for the utilization of Ugi-azide to produce an azasugar-tetrazole which may represent an important biological motif. Herein, we report an efficient one-pot method for the installation of a tetrazolyl at the C-1 position of the piperidine ring, by nucleophilic addition of isocyanides to an in situ generated iminium ion,¹¹ and intermediate nitrilium ion trapping with azide¹²

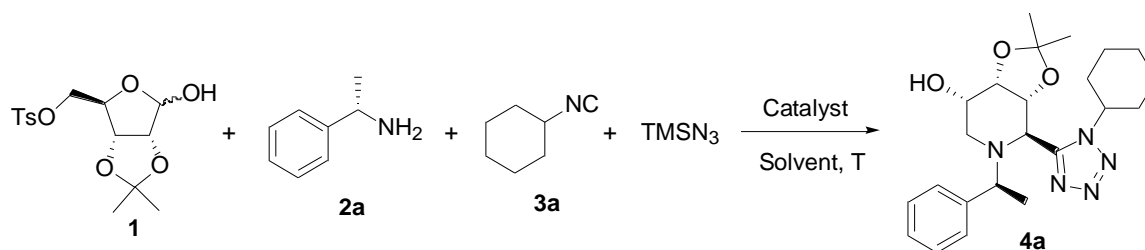
(Scheme 1).



Scheme 1. Synthesis of novel *N*-substituted α -tetrazolyl azasugars

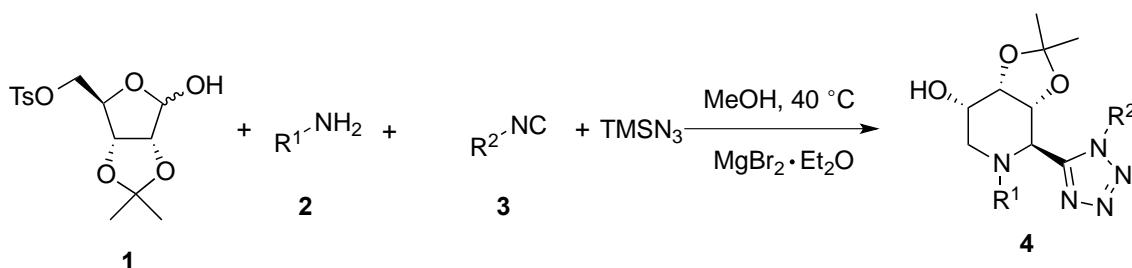
To obtain the *N*-substituted azasugar-tetrazole **4a**, the reaction was carried out with excess amount of (*S*)-1-phenylethylamine (**2a**), cyclohexyl isocyanide (**3a**), and trimethylsilyl azide in methanol without catalyst at room temperature. In this condition, the reaction took place smoothly to afford the expected adduct **4a** in 65% yield at 10 h. It is well known that Lewis acids could help the activation of the Schiff base and its formation which could be the rate-limiting step in the Ugi-4CR.¹³ Hence, we initiated our work by screening various acids such as *p*-TsOH, $Mg(OTf)_2$, $MgBr_2 \cdot Et_2O$, AgOTf, and $BF_3 \cdot Et_2O$ as the catalyst in the Ugi-azide reaction. We found that $MgBr_2 \cdot Et_2O$ could produce **4a** in 80% yield, which acts as the superior catalyst (Table 1, entry 4). Screening of solvents showed that methanol gave the best yield of the product, but when hexafluoroisopropanol acts as the reagent, **4a** could not be obtained, instead of nucleophilic substitution of **1** with **2a** (Table 1, entry 10).

With the optimized conditions in hand, we then extended the scope of substrates to different amines and isocyanides. The results at this scope are summarized in Table 2. Firstly, various benzylamines including α -substituted chiral benzylamines (**2a**, **2e**), aromatic mono-substituted benzylamine **2c**, aromatic di-substituted benzylamine **2d** and benzylamine **2b**, with D-ribose tosylate **1**, isocyanides (**3a**, **3b**) and trimethylsilyl azide could smoothly give the corresponding *N*-substituted azasugar derivatives containing α -tetrazolyl (**4a-4g**) in moderate to good yields (Table 2, entries 1-7). Secondly, alkylamines such as *n*-butylamine **2f**, with D-ribose tosylate **1**, isocyanide **3b** and trimethylsilyl azide, could also be employed to afford the azasugar derivative **4h** (Table 2, entry 8). However, no target product was obtained when aniline was used, possibly due to their poor nucleophilicity.

Table 1. Synthesis of the **4a** under various conditions^a

Entry	Solvent	Catalyst	T (°C)	Yield (%) ^b
1	MeOH	-	rt	65
2	MeOH	<i>p</i> -TsOH	rt	55
3	MeOH	Mg(OTf) ₂	rt	68
4	MeOH	MgBr ₂ ·Et ₂ O	rt	78
5	MeOH	AgOTf	rt	66
6	MeOH	BF ₃ ·Et ₂ O	rt	68
7	MeOH	MgBr ₂ ·Et ₂ O	40	80
8	MeCN	MgBr ₂ ·Et ₂ O	40	62
9	CHCl ₃	MgBr ₂ ·Et ₂ O	40	55
10	(CF ₃) ₂ CHOH	MgBr ₂ ·Et ₂ O	rt	trace

^a Reaction condition: **1** (1.0 mmol), **2a** (2.0 mmol), **3a** (1.0 mmol), TMSN_3 (1.0 mmol). ^b Yield of isolated products.

Table 2. Synthesis of *N*-substituted azasugar-tetrazoles from tosyl D-ribose **1** with amines **2a-f**, isocyanides **3a-b** and TMSN_3 ^a

Entry	R ¹	R ²	Yield (%) ^b	Time (h)	Product
1	L-1-phenylethyl (2a)	cyclohexyl (3a)	80	18	4a
2	L-1-phenylethyl (2a)	<i>t</i> -butyl (3b)	85	18	4b
3	benzyl (2b)	<i>t</i> -butyl (3b)	68	18	4c
4	<i>p</i> -Me-phenyl (2c)	cyclohexyl (3a)	82	18	4d
5	2,4-difluorobenzyl (2d)	cyclohexyl (3a)	84	18	4e
6	2,4-difluorobenzyl (2d)	<i>t</i> -butyl (3b)	88	18	4f
7	(1 <i>R</i>)-2-hydroxy-1-phenylethyl (2e)	<i>t</i> -butyl (3b)	58	24	4g
8	<i>n</i> -butyl (2f)	<i>t</i> -butyl (3b)	56	24	4h

^a All reactions were performed with 1.45 mmol of tosyl D-ribose **1a**, 2.90 mmol of amine **2**, 1.45 mmol of $\text{MgBr}_2 \cdot 2\text{Et}_2\text{O}$, 1.45 mmol of isocyanide **3** and 1.45 mmol TMSN_3 . ^b Isolated yield.

In conclusion, we have developed a Ugi-azide reaction promoted by $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$ using D-ribose tosylate, alkylamines, isocyanides, and azidotrimethylsilane, which afforded a series of *N*-alkyl substituted azasugar-tetrazole hybrid molecules in moderate to good yields (56~88%). This methodology provides convenient access to the synthesis of a wide variety of *N*-substituted azasugar derivatives as potential glucosidase inhibitors. The investigations of the biological activities of these compounds will be undertaken.

EXPERIMENTAL

Reactions were monitored by thin layer chromatography (TLC) using commercial silica gel HSGF254 plates. TLC spots were viewed under ultraviolet light and by heating the plate after treatment with a 5% sulphuric acid in EtOH (v/v). Product purification by gravity column chromatography was performed using commercial silica gel HG/T2354-92 (200-300 mesh). ^1H and ^{13}C NMR (400 and 100 MHz, respectively) spectra were recorded in CDCl_3 , and TMS was used as an internal standard. Solvents and reagents were obtained from commercial suppliers and were used without further purification.

General procedure for the synthesis of *N*-substituted azasugar-tetrazole hybrid molecules 4a-h.

To a stirred solution of **1** (0.5 g, 1.45 mmol) in dry MeOH (10 mL), R^1NH_2 (2.9 mmol, 2 equiv.), $\text{MgBr}_2 \cdot 2\text{Et}_2\text{O}$ (0.5 g, 1.45 mmol) were mixed, and isocyanide (1.45 mmol) and trimethylsilyl azide (1.45 mmol) were added after 30 min. The mixture was stirred at 40 °C until the reaction was complete (as monitored by TLC). The mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic layer was washed with saturated aqueous NaCl solution and dried over anhydrous Na_2SO_4 . The solvent was evaporated and the residue was purified by column chromatography over silica gel ($V_{\text{EtOAc}}:V_{\text{Hexane}}=1:2$) afforded **4**.

(3aR,4R,7S,7aS)-4-(1-Cyclohexyl-1H-tetrazol-5-yl)-2-methyl-5-((R)-1-phenylethyl)hexahydro[1,3]dioxolo[4,5-c]pyridin-7-ol (4a). Obtained as a white solid, yield 80%. mp 154-156 °C, ^1H NMR (400 MHz, CDCl_3) δ 7.40 (d, $J = 7.6$ Hz, 2H), 7.33-7.23 (m, 3H), 4.52 (t, $J = 9.4$ Hz, 1H), 4.45-4.42 (m, 1H), 4.36-4.29 (m, 1H), 4.15 (d, $J = 7.3$ Hz, 1H), 4.02 (s, 1H), 3.63 (d, $J = 7.1$ Hz, 1H), 2.80-2.75 (m, 1H), 2.58-2.52 (m, 1H), 2.21-2.11 (m, 2H), 2.01-1.90 (m, 6H), 1.78 (d, $J = 8.1$ Hz, 2H), 1.65 (s, 3H), 1.37 (s, 3H), 1.26 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.2, 141.9, 128.3, 127.5, 127.2, 110.2, 78.1, 74.9, 66.0, 58.2, 57.1, 46.4, 33.6, 33.0, 27.9, 25.8, 25.50, 25.3, 24.7. TOF MS ES^+ 428.2639 (M+H).

(3aR,4R,7S,7aS)-4-(1-*t*-Butyl-1H-tetrazol-5-yl)-2-methyl-5-((R)-1-phenylethyl)hexahydro[1,3]dioxolo[4,5-c]pyridin-7-ol (4b). Obtained as a colorless syrup, yield 85%. ^1H NMR (400 MHz, CDCl_3) δ 7.40 (d, $J = 7.4$ Hz, 2H), 7.30-7.18 (m, 3H), 4.66 (d, $J = 5.3$ Hz, 1H), 4.52 (t, $J = 11.4$ Hz, 1H), 4.36 (t, $J = 10.4$ Hz, 1H), 4.09 (t, $J = 7.4$ Hz, 1H), 3.64-3.59 (m, 1H), 3.01 (dd, $J = 11.7, 4.3$ Hz, 1H), 2.73 (dd, $J = 11.6, 8.7$ Hz, 1H), 1.74 (s, 9H), 1.60 (s, 3H), 1.33 (s, 3H), 1.31 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz,

CDCl₃) δ 155.8, 142.9, 128.3, 127.6, 127.1, 109.7, 78.4, 74.3, 65.7, 62.4, 57.9, 56.8, 45.9, 30.6, 27.1, 25.3. TOF MS ES⁺ 402.2502 (M+H).

(3aR,4R,7S,7aS)-4-(1-*t*-Butyl-1H-tetrazol-5-yl)-2-methyl-5-benzylhexahydro[1,3]dioxolo[4,5-*c*]pyridin-7-ol (4c). Obtained as a colorless syrup, yield 68%. ¹H NMR (400 MHz, CDCl₃) δ 7.31-7.15 (m, 5H), 4.88 (dd, *J* = 7.1, 5.7 Hz, 1H), 4.55 (dd, *J* = 5.8, 4.3 Hz, 1H), 4.51 (d, *J* = 7.0 Hz, 1H), 4.16 (m, 1H), 3.49-3.36 (m, 2H), 3.12 (dd, *J* = 12.6, 4.6 Hz, 1H), 2.69 (dd, *J* = 12.6, 8.3 Hz, 1H), 1.77 (s, 9H), 1.58 (s, 3H), 1.37 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 154.3, 137.7, 128.6, 128.5, 127.5, 109.8, 76.8, 74.7, 64.7, 62.2, 58.4, 56.5, 51.3, 30.5, 27.5, 25.6. TOF MS ES⁺ 388.2312 (M+H).

(3aR,4R,7S,7aS)-4-(1-Cyclohexyl-1H-tetrazol-5-yl)-2-methyl-5-(4-methylbenzyl)hexahydro[1,3]dioxolo[4,5-*c*]pyridin-7-ol (4d). Obtained as a colorless syrup, yield 82%. ¹H NMR (400 MHz, CDCl₃) δ 7.09 (s, 4H), 4.54 (t, *J* = 4.6 Hz, 1H), 4.46 (dd, *J* = 7.3, 5.1 Hz, 1H), 4.36-4.27 (m, 1H), 4.16-4.06 (m, 1H), 3.90 (d, *J* = 7.3 Hz, 1H), 3.46 (d, *J* = 13.1 Hz, 1H), 3.17 (d, *J* = 13.1 Hz, 1H), 3.03 (dd, *J* = 11.6, 4.8 Hz, 1H), 2.52-2.41 (m, 1H), 2.31 (s, 3H), 2.11 (t, *J* = 12.1 Hz, 1H), 1.99-1.90 (m, 5H), 1.79-1.75 (m, 1H), 1.62 (s, 3H), 1.44-1.28 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 153.4, 137.3, 133.7, 129.2, 128.7, 110.3, 77.3, 74.9, 65.5, 59.1, 58.2, 52.4, 33.4, 32.8, 27.8, 25.9, 25.40, 24.8, 21.1. TOF MS ES⁺ 428.2608 (M+H).

(3aR,4R,7S,7aS)-4-(1-Cyclohexyl-1H-tetrazol-5-yl)-2-methyl-5-(2,4-difluorobenzyl)hexahydro[1,3]dioxolo[4,5-*c*]pyridin-7-ol (4e). Obtained as a colorless syrup, yield 84%. ¹H NMR (400 MHz, CDCl₃) δ 7.34 (dd, *J* = 8.5, 6.7 Hz, 1H), 6.89-6.80 (m, 1H), 6.80-6.71 (m, 1H), 4.55 (t, *J* = 4.7 Hz, 1H), 4.50 (dd, *J* = 6.8, 5.2 Hz, 1H), 4.42-4.28 (m, 1H), 4.11 (dt, *J* = 10.7, 4.1 Hz, 1H), 3.90 (d, *J* = 6.8 Hz, 1H), 3.45 (d, *J* = 13.3 Hz, 1H), 3.32 (d, *J* = 13.4 Hz, 1H), 2.94 (dd, *J* = 11.7, 4.8 Hz, 1H), 2.51 (dd, *J* = 11.7, 9.7 Hz, 1H), 2.18-2.07 (m, 1H), 2.05-1.93 (m, 5H), 1.81-1.75 (m, 1H), 1.62 (s, 3H), 1.36 (d, *J* = 10.6 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 153.4, 132.2, 129.9, 128.0, 113.0, 103.9, 77.3, 74.7, 65.3, 59.2, 52.0, 32.9, 27.8, 26.5, 25.8. TOF MS ES⁺ 450.2212 (M+H).

(3aR,4R,7S,7aS)-4-(1-*t*-Butyl-1H-tetrazol-5-yl)-2-methyl-5-(2,4-difluorobenzyl)hexahydro[1,3]dioxolo[4,5-*c*]pyridin-7-ol (4f). Obtained as a colorless syrup, yield 88%. ¹H NMR (400 MHz, CDCl₃) δ 7.22 (d, *J* = 8.5 Hz, 1H), 6.83-6.69 (m, 2H), 4.91 (t, *J* = 6.5 Hz, 1H), 4.57 (t, *J* = 10.8 Hz, 1H), 4.49 (d, *J* = 7.2 Hz, 1H), 4.20 (p, *J* = 4.4 Hz, 1H), 3.61 (d, *J* = 13.5 Hz, 1H), 3.33 (d, *J* = 13.5 Hz, 1H), 3.06 (dd, *J* = 12.7, 4.8 Hz, 1H), 2.73 (dd, *J* = 12.7, 8.5 Hz, 1H), 1.77 (s, 9H), 1.57 (s, 3H), 1.38 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 154.1, 145.0, 131.8, 131.7, 130.0, 128.1, 120.8, 120.7, 113.0, 111.4, 109.9, 104.0, 78.3, 74.6, 68.0, 62.3, 58.4, 51.3, 48.5, 30.4, 29.7, 27.5, 26.5. TOF MS ES⁺ 424.2108 (M+H).

(3aR,4R,7S,7aS)-4-(1-*t*-Butyl-1H-tetrazol-5-yl)-2-methyl-5-((*S*)-2-hydroxy-1-phenylethyl)hexahydro[1,3]dioxolo[4,5-*c*]pyridin-7-ol (4g). Obtained as a colorless syrup, yield 58%. ¹H NMR (400 MHz, CDCl₃) δ 7.42-7.31 (m, 1H), 7.25-7.14 (m, 2H), 7.14-7.06 (m, 2H), 5.15 (d, *J* = 3.2 Hz, 1H), 4.36 (dd, *J* = 6.8, 4.7 Hz, 1H), 4.31 (dd, *J* = 6.7, 3.3 Hz, 1H), 4.19 (m, 1H), 4.00 (dd, *J* = 9.5, 4.0 Hz, 1H), 3.97-3.90 (m,

1H), 3.82 (dd, $J = 11.5, 4.4$ Hz, 1H), 3.63 (dd, $J = 13.1, 2.7$ Hz, 1H), 3.21 (dd, $J = 13.1, 5.6$ Hz, 1H), 1.66 (s, 9H), 1.57 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 155.4, 139.4, 129.0, 128.5, 128.0, 127.5, 109.4, 77.3, 76.1, 73.1, 67.0, 65.0, 62.7, 56.3, 43.9, 30.30, 26.4, 24.9. TOF MS ES^+ 418.2408 (M+H).

(3aR,4R,7S,7aS)-4-(1-*t*-Butyl-1H-tetrazol-5-yl)-2-methyl-5-(*n*-butyl)hexahydro[1,3]dioxolo[4,5-*c*]pyridin-7-ol (4h). Obtained as a colorless syrup, yield 56%. ^1H NMR (400 MHz, CDCl_3) δ 4.89 (dd, $J = 7.4, 5.6$ Hz, 1H), 4.57-4.51 (m, 1H), 4.35 (dd, $J = 7.6, 1.3$ Hz, 1H), 4.23 (m, 1H), 3.24 (dd, $J = 12.8, 4.6$ Hz, 1H), 2.74 (dd, $J = 12.7, 8.8$ Hz, 1H), 2.23 (d, $J = 9.0$ Hz, 2H), 1.78 (s, 9H), 1.53 (s, 3H), 1.37 (s, 3H), 1.32 (m, 4H), 0.77 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.0, 110.5, 109.7, 77.3, 76.0, 74.8, 73.6, 64.1, 62.2, 58.5, 56.8, 51.8, 51.1, 50.8, 30.3, 30.2, 30.2, 29.9, 29.7, 27.6, 25.6, 24.4, 20.1, 20.0, 13.9, 13.8. TOF MS ES^+ 353.2452 (M+H).

ACKNOWLEDGEMENTS

We are grateful for the financial support from Guizhou Engineering Research Center (QJHKYZ[2017]024, Cooperation Project with Science and Technology of Guizhou Province (QKHLHZ[2016]7309 and QKHLHZ[2015]7234), and Doctoral Scientific Research Foundation of Tongren university (trxyDH1605).

REFERENCES

1. C. Decroocq, F. Stauffert, O. Pamard, F. Oulaidi, E. Gallienne, and O. R. Martin, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 830.
2. A. A. Watson, G. W. J. Fleet, N. Asano, R. J. Molyneux, and R. J. Nash, *Phytochemistry*, 2001, **56**, 265.
3. D. Durantel, N. Branza-Nichita, S. Carrouee-Durantel, T. D. Butters, R. A. Dwek, and N. Zitzmann, *J. Virol.*, 2001, **75**, 8987.
4. P. Compain and O. R. Martin, *Iminosugars: from Synthesis to Therapeutic Applications*, Wiley-VCH, Weinheim, 2007.
5. A. Mitrakou, N. Tountas, A. E. Raptis, R. J. Bauer, H. Schulz, and S. A. Raptis, *Diab. Med.*, 1998, **15**, 657.
6. T. D. Butters, R. A. Dwek, and F. M. Platt, *Curr. Top. Med. Chem.*, 2003, **3**, 561.
7. (a) A. Kato, I. Nakagome, S. Nakagawa, K. Kinami, I. Adachi, S. F. Jenkinson, J. Desire, Y. Bleriot, R. J. Nash, G. W. J. Fleet, and S. Hirono, *Org. Biomol. Chem.*, 2017, **15**, 9297; (b) B. J. Ayers, A. F. G. Glawar, R. F. Martinez, N. Ngo, Z. Liu, G. W. J. Fleet, T. D. Butters, R. J. Nash, C. Y. Yu, M. R. Wormald, S. Nakagawa, I. Adachi, A. Kato, and S. F. Jenkinson, *J. Org. Chem.*, 2014, **79**, 3398.

8. C. K. Lin, L. W. Cheng, H. Y. Li, W. Y. Yun, and W. C. Cheng, [*Org. Biomol. Chem.*, 2015, **13**, 2100.](#)
9. A. Dömling, [*Chem. Rev.*, 2006, **106**, 17.](#)
10. (a) T. Nixey, M. Kelly, and C. Hulme, [*Tetrahedron Lett.*, 2000, **41**, 8729](#); (b) T. Nixey, M. Kelly, D. Semin, and C. Hulme, [*Tetrahedron Lett.*, 2002, **43**, 3681](#); (c) M. Nayak and S. Batra, [*Tetrahedron Lett.*, 2010, **51**, 510](#); (d) R. S. Borisov, A. I. Polyakov, L. A. Medvedeva, V. N. Khrustalev, N. I. Guranova, and L. G. Voskressensky, [*Org. Lett.*, 2010, **12**, 3894](#); (e) C. Kalinski, M. Umkehrer, S. Gonnard, N. Jager, G. Ross, and W. Hiller, [*Tetrahedron Lett.*, 2006, **47**, 2041.](#)
11. (a) S. Senthilkumar, S. S. Prasad, P. S. Kumar, and S. Baskaran, [*Chem. Commun.*, 2014, **50**, 1549](#); (b) S. Senthilkumar, S. S. Prasad, A. Das, and S. Baskaran, [*Chem. Eur. J.*, 2015, **21**, 15914](#); (c) S. S. Prasad, S. Senthilkumar, A. Srivastava, and S. Baskaran, [*Org. Lett.*, 2017, **19**, 4403](#); (d) X. G. Hu, A. D. Ariawan, and L. Hunter, [*Tetrahedron Lett.*, 2014, **55**, 7222](#); (e) W. Yuan, J. Xia, X. Zhang, P. Liang, J. Zhang, W. Jiao, and H. Shao, [*Tetrahedron*, 2016, **72**, 3994.](#)
12. T. Nixey, M. Kelly, D. Semin, and C. Hulme, [*Tetrahedron Lett.*, 2002, **43**, 3681.](#)
13. Y. Wang, P. Patil, K. Kurpiewska, J. Kalinowska-Tluscik, and A. Mling, [*ACS Comb. Sci.*, 2017, **19**, 193.](#)