OL | Organic Letters

pubs.acs.org/OrgLett Letter

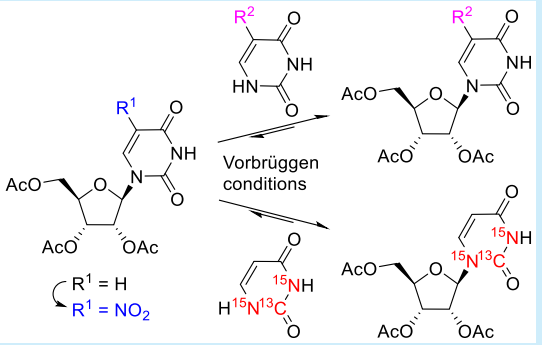
Transglycosylation in the Modification and Isotope Labeling of Pyrimidine Nucleosides

Yong Gong,* Lu Chen, Wei Zhang, and Rhys Salter

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01941 Read Online

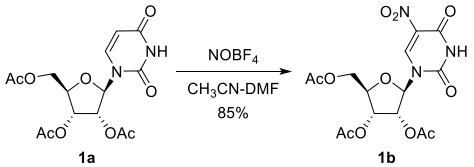
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Transglycosylation of pyrimidine nucleosides is demonstrated in a one-pot synthesis of uridine derivatives under microwave irradiation. Inductive activation of 2′,3′,5′-tri-*O*-acetyl uridine with a 5-nitro group produces a more-reactive glycosyl donor. Under optimized Vorbrüggen conditions, the 5-nitrouridine facilitates a reversible nucleobase exchange with a series of 5-substituted uracils. The protocol is also exemplified in a gram-scale reaction under thermal heating. The strategy provides easy access to isotopically labeled uridine.



Nucleoside derivatives have shown therapeutic potential in the development of anticancer and antiviral agents.[1,2] Various synthetic approaches to nucleosides are available.[3] The most common method makes use of the Vorbrüggen glycosylation,[4] which couples silylated nucleobases with glycosyl donors in the presence of a Lewis acid. Ribose acetates are the prevailing glycosyl donors for glycosylation. Other activated riboses, Lewis acids, and silylating reagents have also been reported.[5−7] Transglycosylation is an extremely efficient strategy for late-stage incorporation of modified nucleobases.[8−10] Kinetically controlled enzymatic transglycosylation has been used commonly in the biosynthesis of nucleosides.[11] Enzyme-guided specific nucleobase exchange from cytosine to thymine in RNA has been reported for gene editing.[12] Thermodynamically controlled chemical transglycosylation within or between purines and pyrimidines has also been reported.[13] Recently, bridge-locked thymine nucleosides were effectively transglycosylated to adenine, guanine, and methylcytosine nucleosides.[14] However, transglycosylation of 3′,5′-dibenzoyl-2′-deoxy-L-uridine with excess silylated 5-fluorouracil afforded low yields of the corresponding α- and β-deoxyfluorouridines,[15] which could be attributed partially to the weak reactivity of the starting deoxyuridine and the poor nucleophilicity of the fluoropyrimidine base.

For nucleosides containing complex ribose parts, the conventional glycosylation approach with ribose acetates as glycosyl donors may face greater challenges requiring significant investment in either the synthesis of unnatural ribose acetates or derivatization of natural/simple nucleosides. It would be ideal if a readily available and less-reactive parent nucleoside could be activated via a simple chemical derivatization. The resulting activated nucleoside, in turn, could act as a better glycosyl donor and undergo the thermodynamically more favored transglycosylation with a target nucleobase to form a desired nucleoside. The proposed activation exchange may be applied as an alternative to the conventional approach in the late-stage or final-stage modification of nucleosides. In this paper, 2′,3′,5′-tri-*O*-acetyl uridine (**1a**) was used as the starting nucleoside for a proof-of-concept study. A nitro activating group was selected for its well-known strong inductive effect. The inductive activation was realized via a simple nitration[16,17] of uridine **1a** with nitrosyl tetrafluoroborate ($NOBF_4$) to 5-nitrouridine **1b** (see eq 1).



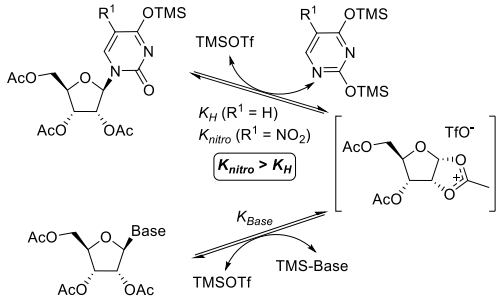
(1)

Based on the known mechanism of transglycosylation[10a] (Scheme 1), it is reasonable to envision that, under Vorbrüggen glycosylation conditions, the silylated form of uridine **1a** or nitrouridine **1b** equilibrates with a neighboring 2′-*O*-acyl group participated dioxolenium intermediate and a silyloxy-pyrimidine or silyloxy-nitropyrimidine in the presence

Received: June 9, 2020

https://dx.doi.org/10.1021/acs.orglett.0c01941
Org. Lett. XXXX, XXX, XXX−XXX

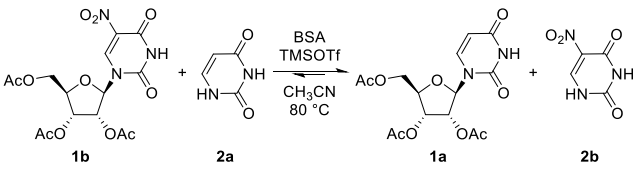
Scheme 1. Mechanism-Based Inductive Activation Strategy



of trimethylsilyl trifluoromethansulfonate (TMSOTf). The strong electron-withdrawing ability of the 5-nitro group can make the outgoing silyloxy-nitropyrimidine a better leaving group and the departed silyloxy-nitropyrimidine a weaker nucleophile.[18] The equilibrium constant K_{nitro} (R^1 = NO_2) should be greater than K_H (R^1 = H). The common cation intermediate can react reversibly with any silylated nucleobase to form a new glycoside with an equilibrium constant K_{Base}. The thermodynamically controlled equilibrium is determined by the ratio of K_H:K_{Base} or K_{nitro}:K_{Base}. The inductive activation by a 5-nitro group should drive the competition toward transglycosylation (K_{nitro}:K_{Base} > K_H:K_{Base}).[10c]

Microwave (μW) irradiation[19] was used in this research and compared with thermal heating. The equilibrium conditions for one-pot transglycosylation of 5-nitrouridine **1b** with uracil (**2a**) to uridine **1a** and 5-nitrouracil (**2b**) in acetonitrile were screened (see Table 1). Quenching of each reaction occurred during reverse-phase quantitative HPLC analysis.[20] The yield of **1a** and conversion of **1b** were calibrated with authentic **1a** and **1b** standards. At a **1b**:**2a** ratio of 1:1, 3 equiv of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and 1.5 equiv of TMSOTf gave a peak yield (58%) of **1a** within 2 h under an 80 °C oil bath (Table 1, entries 1 and 2). Under microwave heating at 80 °C, the yield improved (67%) within 1 h (Table 1, entry 4).

Table 1. One-Pot Transglycosylation Equilibrium Conditions



entry	**1b**:**2a**:BSA:TMSOTf[a]	time (h)	yield[b] (%)
1	1:1:3:1.5	1[c]	41 (45)
2	1:1:3:1.5	2[c]	58 (63)
3	1:1:3:1.5	3[c]	59 (68)
4	**1:1:3:1.5**	**1**[d]	**67 (71)**
5	1:1:3:1.5	2[d]	65 (80)
6	1:1:2.5:1.3	1[d]	61 (69)
7	1:1:3:0.5	1[d]	23 (26)
8	1:1:1.5:1.5	1[d]	17 (17)
9	1:1:4.5:1.5	1[d]	36 (98)
10	1:2:4.5:1.5	1[d]	43 (48)
11	**1:2:5:3**	**1**[d]	**80 (88)**
12	**2:1:3:3**	**1**[d]	**88 (60)**[e]

[a]0.10 mmol **1b**, 1.0 mL CH_3CN. [b]HPLC yield of **1a**. Conversion of **1b** given in parentheses. Calibrated with **1a** and **1b** standards. [c]In a preheated oil bath. [d]Under μW. [e]**2a** as the limiting reagent.

Prolongation of the reaction time (Table 1, entries 3 and 5) increased the conversion of **1b**; however, it did not improve the yield of **1a**. Microwave heating resulted in a slightly improved yield while reducing the heating time (Table 1, entry 4 vs entry 2) and, hence, was used in the further optimization of reaction conditions. Slight reduction of BSA from 3 equiv to 2.5 equiv and TMSOTf from 1.5 equiv to 1.3 equiv was tolerated (Table 1, entry 6). Further reduction of TMSOTf to 0.5 equiv (Table 1, entry 7) or BSA to 1.5 equiv (Table 1, entry 8) decreased the yield of **1a** and conversion of **1b** sharply. Increasing BSA to 4.5 equiv (Table 1, entry 9) resulted in the reduction of **1a** (36%) and the almost-complete loss of **1b** (98%). The presence of excessive BSA caused deglycosylation by *N*-glycosylation of BSA[5a] and competed with the transglycosylation.

Increasing the ratio of **1b**:**2a** alone from 1:1 (Table 1, entry 9) to 1:2 (Table 1, entry 10) had less effect on the yield of **1a**. However, it normalized the conversion of **1b** from 98% to 48% by scavenging the excessive amount of BSA with **2a**. Further adjustment of BSA to 5 equiv and TMSOTf to 3 equiv (Table 1, entry 11) improved the yield of **1a** to 80%. Reversely, at a **1b**:**2a** ratio of 2:1, the yield of **1a** reached 88%, after the amounts of both TMSOTf and BSA were set at 3 equiv (Table 1, entry 12).

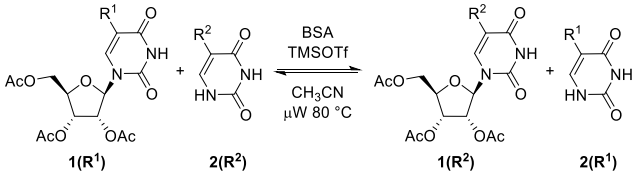
The transglycosylation from **1b** to **1a** was regio (N^3-) and anomerically (β-) selective, which was in agreement with *N*-glycosylation of uracils using known glycosyl donors, since the same reactive dioxolenium intermediate was involved in the glycosylation.[10a] Trace N^1,N^3-bisglycoside byproduct[6b] of **2a**, which represented 0.9% of the total HPLC peak area at 254 nm from the reaction described in entry 4 in Table 1, was detected by liquid chromatography−mass spectroscopy (LC−MS), but not isolated for further characterization. Increasing the amount of **2a** reduced bisglycosidation, while increasing the amount of **1b**, and prolonging the reaction time increased bisglycosidation.

The reactivity of uridines **1**($\mathbf{R^1}$) and the nucleophilicity of uracils **2**($\mathbf{R^2}$) on the equilibration were further examined (see Table 2). Under the standard conditions for a **1**($\mathbf{R^1}$):**2**($\mathbf{R^2}$) ratio of 1:1, uridine **1a** was less reactive with less nucleophilic 5-nitrouracil (**2b**) and 5-bromouracil (**2c**). The equilibration disfavored 5-nitrouridine **1b** (Table 2, entry 1) and 5-bromouridine **1c** (Table 2, entry 3) with an equilibrated molar ratio of 1:3.0 for **1b**:**1a** and 1:3.3 for **1c**:**1a**. Conversely, **1b** (Table 2, entry 2) and **1c** (Table 2, entry 4) equilibrated favorably toward **1a** with a ratio of 1:2.3 for **1b**:**1a** and 1:3.3 for **1c**:**1a**. The constant **1c**:**1a** ratios in entries 3 and 4 in Table 2 reflected the establishment of the equilibration. The lower **1b**:**1a** ratio in entry 1 in Table 2 (1:3.0) than in entry 2 in Table 2 (1:2.3) indicated that more deglycosylation of **1b** occurred. The glycosyl donating ability of **1b** was comparable to **1c**, as reflected by the similar yields of **1a** in entries 2 and 4 in Table 2. The inductive activation plateaued under tested conditions. **1b** and **1c** reached an equilibrium in almost 1:1 ratio (Table 2, entry 5). Besides 5-nitro group, a 5-halo group (Br, Cl, or I) could also be easily introduced into uridine **1a** via direct halogenation[21] for potential activation and transglycosylation applications.

At a **1**($\mathbf{R^1}$):**2**($\mathbf{R^2}$) ratio of 1:2, the equilibrium in entry 6 in Table 2, as expected, was driven further by **2a** from **1b** to **1a**. However, more deglycosylation of **1a** and **1b** occurred with less nucleophilic **2b** in entry 7 in Table 2. Transglycosylation of **1a** (Table 2, entry 8) and **1b** (Table 2, entry 9) with more

https://dx.doi.org/10.1021/acs.orglett.0c01941
Org. Lett. XXXX, XXX, XXX−XXX

Table 2. Reactivity and Nucleophilicity on Equilibration



entry	$1(R^1)$	$2(R^2)$	$1(R^2)$	yield[a] (%)	$1(R^2)$:$1(R^1)$[d]
1	**1a**(H)	**2b**(NO_2)	**1b**(NO_2)	22[b]	1:3.0 (**1b**:**1a**)
2	**1b**(NO_2)	**2a**(H)	**1a**(H)	67[b]	2.3:1 (**1a**:**1b**)
3	**1a**(H)	**2c**(Br)	**1c**(Br)	19[b]	1:3.3 (**1c**:**1a**)
4	**1c**(Br)	**2a**(H)	**1a**(H)	63[b]	3.3:1 (**1a**:**1c**)
5	**1c**(Br)	**2b**(NO_2)	**1b**(NO_2)	48[b]	1:1.1 (**1b**:**1c**)
6	**1b**(NO_2)	**2a**(H)	**1a**(H)	79[c]	11:1 (**1a**:**1b**)
7	**1a**(H)	**2b**(NO_2)	**1b**(NO_2)	19[c]	1:2.1 (**1b**:**1a**)
8	**1a**(H)	**2d**(CH_3)	**1d**(CH_3)	73[c]	2.9:1 (**1d**:**1a**)
9	**1b**(NO_2)	**2d**(CH_3)	**1d**(CH_3)	82[c]	12:1 (**1d**:**1b**)

[a]HPLC yield of $1(R^2)$. Calibrated with the corresponding $1(R^2)$ standards. [b]0.10 mmol $1(R^1)$, $1(R^1)$:$2(R^2)$:BSA:TMSOTf = 1:1:3:1.5, 1 h. [c]0.20 mmol $1(R^1)$, $1(R^1)$:$2(R^2)$:BSA:TMSOTf = 1:2:5:3, 2 h. [d]Equilibrated molar ratio. Calculated from the yield of $1(R^2)$ and the remaining $1(R^1)$.

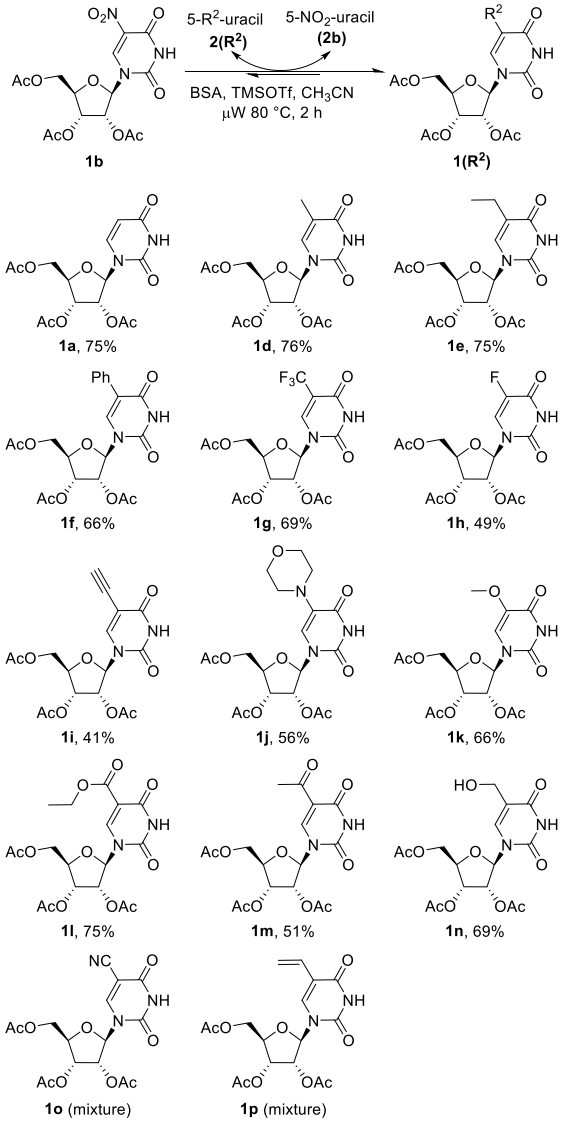
nucleophilic thymidine **2d** gave good yields of 5-methyluridine **1d** and a marginally better yield from **1b**. Higher **1a**:**1b** ratio (11:1) in entry 6 in Table 2 and **1d**:**1b** ratio (12:1) in entry 9 in Table 2 reflected higher reactivity of **1b** under the reaction conditions.

Under the now-optimized conditions stated in Scheme 2, the scope of uracils $2(R^2)$ as nucleobases for the one-pot transglycosylation with 5-nitrouridine **1b** as the glycosyl donor was then examined. Uracil (**2a**), along with 5-methyl, 5-ethyl, 5-phenyl, 5-trifluoromethyl, and 5-fluoro uracils (**2d**–**2h**), gave the corresponding uridines **1a**, **1d**–**1h** in moderate to good isolated yields (49%–76%). Uracils functionalized with 5-ethynyl, 5-morpholino, 5-methoxy, 5-ethoxycarbonyl, 5-acetyl, and 5-hydroxymethyl (**2i**–**2n**) gave the desired uridines (**1i**–**1n**) in 41%–75% isolated yields. The conversions of **1b**, in all cases, were generally >80%. The competing deglycosylation side reactions affected the yields at variable rates. However, some functional groups were not well-tolerated under the standard conditions. 5-Cyanouracil (**2o**) gave a mixture containing both desired 5-cyanouridine **1o** and carboxamide byproduct from partial hydrolyzation of the cyano group. 5-Vinyluracil (**2p**) gave a complicated mixture with poor yield (<10%) of desired 5-vinyluridine **1p**, because of the chemical reactivity of the 5-vinyluracil moiety.[22] The stereochemistry on the 1′ position in product uridines $1(R^2)$ was confirmed by matching NMR data with either published or authentic standards.

From the perspective of a practical synthetic application, a gram-scale reaction of 5-nitrouridine **1b** (2.4 mmol) with thymine (**2d**) was performed at 80 °C in an oil bath for 5 h under the conditions in Scheme 3. An isolated yield of 83% of 5-methyluridine **1d** was obtained after aqueous desilylation and silica column purification, which matched the previous yield from a smaller scale (0.20 mmol) microwave (2 h) reaction at the same temperature.

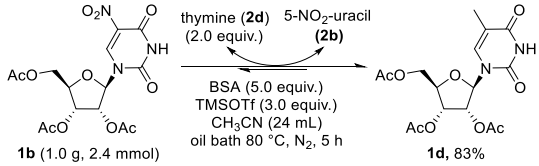
Isotopically labeled nucleosides have been synthesized and used as tool compounds for various applications.[23−26] Direct exchange of uridine **1a** with 1 equiv of uracil isotopologue

Scheme 2. Scope of Transglycosylation[a]



[a]0.20 mmol **1b**, **1b**:$2(R^2)$:BSA:TMSOTf = 1:2:5:3, 2.0 mL of CH_3CN. Isolated yield.

Scheme 3. Gram-Scale Reaction under Oil Bath Heating

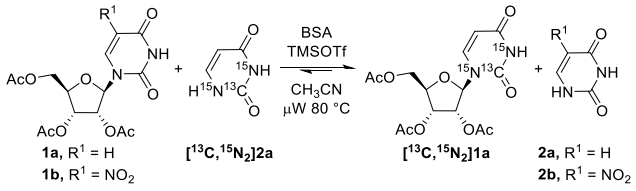


[^{13}C,$^{15}N_2$]**2a** (Table 3, entry 1) produced 50% enriched isotopologue [^{13}C,$^{15}N_2$]**1a** in 42% yield (diluted with 50% unconverted and inseparable **1a**). Equal mass peak areas of [^{13}C,$^{15}N_2$]**1a** and **1a** were observed in LC–MS analysis. When **1a** reacted with 2 equiv [^{13}C,$^{15}N_2$]**2a** (Table 3, entry 2), the yield of 66% enriched [^{13}C,$^{15}N_2$]**1a** improved to 61% (diluted with 34% **1a**), where mass peak area ratio of 2:1 for [^{13}C,$^{15}N_2$]**1a**:**1a** was confirmed by LC–MS.

For high or full isotopic enrichment, activation-exchange approach becomes a viable option. The reaction of 5-nitrouridine **1b** with 1 equiv of [^{13}C,$^{15}N_2$]**2a** produced fully

https://dx.doi.org/10.1021/acs.orglett.0c01941
Org. Lett. XXXX, XXX, XXX−XXX

Table 3. Isotope Labeling via Base Exchange



1a, R^1 = H
1b, R^1 = NO_2
[^{13}C,^{15}N$_2$]2a
[^{13}C,^{15}N$_2$]1a
2a, R^1 = H
2b, R^1 = NO_2

entry	1(R^1)	[^{13}C,^{15}N$_2$]2a (equiv)	yield (%)	1a:[^{13}C,^{15}N$_2$]1a[i]
1	1a	1[a]	42[d,e]	1:1
2	1a	2[b]	61[d,f]	1:2
3	1b	1[a]	63[d]	–
4	1b	2[b]	68[g]	–
5	1b	0.5[c]	74[g,h]	–

[a]1(R^1):BSA:TMSOTf = 1:3:1.5, 2 h. [b]1(R^1):BSA:TMSOTf = 1:5:3, 2 h. [c]1b:BSA:TMSOTf = 2:3:3, 1 h. [d]HPLC yield. Calibrated with 1a standard. [e]Calculated from a 50% enriched isotopic mixture of [^{13}C,^{15}N$_2$]1a and 1a. [f]Calculated from a 66% enriched isotopic mixture. [g]Isolated yield. [h]Based on [^{13}C,^{15}N$_2$]2a. [i]Equilibrated molar ratio. Determined by mass peak area ratio of 1a:[^{13}C,^{15}N$_2$]1a in LC–MS.

enriched [^{13}C,^{15}N$_2$]1a in 63% yield (Table 3, entry 3). Minor unreacted 1b was separable from [^{13}C,^{15}N$_2$]1a. An isolated yield of 68% was achieved when 2 equiv of [^{13}C,^{15}N$_2$]2a was used (Table 3, entry 4). An even higher isolated yield (74%) was obtained when 2 equiv of 1b was used (Table 3, entry 5). 5-Nitrouridine 1b not only improved the exchange yield, but also prevented the isotopic dilution from direct usage of 1a in entries 1 and 2 in Table 3.

The potential isotopic effects on the equilibration were evaluated from the equilibrated 1a:[^{13}C,^{15}N$_2$]1a ratios via LC–MS analysis. The observed 1:1 ratio of 1a:[^{13}C,^{15}N$_2$]1a in entry 1 in Table 3 and the 1:2 ratio in entry 2 in Table 3 indicated the absence of any significant isotopic effect. The marginal difference between the isolated yields of 1a in Scheme 2 and [^{13}C,^{15}N$_2$]1a in entry 4 in Table 3 reflected experimental variations between two reactions.

In summary, the above work has demonstrated the viability of an activation-exchange approach for the modification of pyrimidine nucleosides via inductive activation of parent uridine 1a to 5-nitrouridine 1b as a more reactive glycosyl donor, followed by transglycosylation with substituted uracils. The reactivity of uridines, nucleophilicity of uracil nucleobases, and reaction conditions on exchange equilibration were investigated under microwave irradiation. The optimized Vorbrüggen conditions were used in the synthesis of 5-substituted uridine derivatives. The one-pot protocol was illustrated successfully in a gram-scale conversion under thermal heating. The approach also enabled the fully isotope labeling of the parent uridine 1a. The strategy and developed conditions provide convenient access to nucleoside analogues and isotopologues that can be otherwise difficult to synthesize.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01941.

Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra of all the isolated compounds, and a representative HPLC chromatogram of transglycosylation reaction (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Yong Gong – *Discovery Sciences, Janssen Research & Development, Johnson & Johnson, Spring House, Pennsylvania 19477, United States;* orcid.org/0000-0001-8964-1944; Email: ygong@its.jnj.com

Authors

Lu Chen – *Discovery Sciences, Janssen Research & Development, Johnson & Johnson, Spring House, Pennsylvania 19477, United States*

Wei Zhang – *Discovery Sciences, Janssen Research & Development, Johnson & Johnson, Spring House, Pennsylvania 19477, United States*

Rhys Salter – *Discovery Sciences, Janssen Research & Development, Johnson & Johnson, Spring House, Pennsylvania 19477, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01941

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful to Ronghui Lin and Fengbin Song (Discovery Sciences, Janssen Research & Development, Johnson & Johnson) for their helpful chemistry discussions.

■ REFERENCES

(1) *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C. K., Baker, D. C., Eds.; Plenum Press: New York, 1993.

(2) (a) De Clercq, E.; Li, G. *Clin. Microbiol. Rev.* **2016**, *29*, 695–747. (b) Jordan, P. C.; Stevens, S. K.; Deval, J. *Antivir. Chem. Chemother.* **2018**, *26*, 1–19.

(3) (a) *Chemical Synthesis of Nucleoside Analogues*; Merino, P., Ed.; Wiley: Hoboken, NJ, 2013. (b) Downey, A. M.; Richter, C.; Pohl, R.; Mahrwald, R.; Hocek, M. *Org. Lett.* **2015**, *17*, 4604–4607.

(4) Vorbrüggen, H.; Ruh-Pohlenz, C. *Org. React.* **1999**, *55*, 1–630.

(5) (a) Liao, J.; Sun, J.; Yu, B. *Tetrahedron Lett.* **2008**, *49*, 5036–5038. (b) Yu, B.; Sun, J. *Chem. Commun.* **2010**, *46*, 4668–4679. (c) Rao, B. V.; Manmode, S.; Hotha, S. *J. Org. Chem.* **2015**, *80*, 1499–1505.

(6) (a) Zhang, Q.; Sun, J.; Zhu, Y.; Zhang, F.; Yu, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 4933–4936. (b) Shirouzu, H.; Morita, H.; Tsukamoto, M. *Tetrahedron* **2014**, *70*, 3635–3639. (c) Basu, N.; Oyama, K.; Tsukamoto, M. *Tetrahedron Lett.* **2017**, *58*, 1921–1924.

(7) Bozhok, T. S.; Sivets, G. G.; Baranovsky, A. V.; Kalinichenko, E. N. *Tetrahedron* **2016**, *72*, 6518–6527.

(8) (a) Crisp, G. T.; Flynn, B. L. *Tetrahedron Lett.* **1990**, *31*, 1347–1350. (b) Flynn, B. L.; Macolino, V.; Crisp, G. T. *Nucleosides Nucleotides* **1991**, *10*, 763–779.

(9) (a) Nowak, I.; Robins, M. J. *Org. Lett.* **2005**, *7*, 4903–4905. (b) Nowak, I.; Cannon, J. F.; Robins, M. J. *Org. Lett.* **2006**, *8*, 4565–4568. (c) Klier, L.; Aranzamendi, E.; Ziegler, D.; Nickel, J.; Karaghiosoff, K.; Carell, T.; Knochel, P. *Org. Lett.* **2016**, *18*, 1068–1071.

(10) (a) Boryski, J. *Curr. Org. Chem.* **2008**, *12*, 309–325. (b) Lapponi, M. J.; Rivero, C. W.; Zinni, M. A.; Britos, C. N.; Trelles, J. A. *J. Mol. Catal. B: Enzym.* **2016**, *133*, 218–233. (c) Kaspar, F.; Giessmann, R. T.; Hellendahl, K.; Neubauer, P.; Wagner, A.; Gimpel, M. *ChemBioChem* **2020**, *21*, 1428–1432.

(11) (a) Hatano, A.; Kurosu, M.; Yonaha, S.; Okada, M.; Uehara, S. *Org. Biomol. Chem.* **2013**, *11*, 6900–6905. (b) Drenichev, M. S.; Alexeev, C. S.; Kurochkin, N. N.; Mikhailov, S. N. *Adv. Synth. Catal.* **2018**, *360*, 305–312. (c) Alexeev, C. S.; Drenichev, M. S.; Dorinova,

https://dx.doi.org/10.1021/acs.orglett.0c01941
Org. Lett. XXXX, XXX, XXX–XXX

E. O.; Esipov, R. S.; Kulikova, I. V.; Mikhailov, S. N. *Biochim. Biophys. Acta, Proteins Proteomics* **2020**, *1868*, 140292.
(12) Abudayyeh, O. O.; Gootenberg, J. S.; Franklin, B.; Koob, J.; Kellner, M. J.; Ladha, A.; Joung, J.; Kirchgatterer, P.; Cox, D. B. T.; Zhang, F. *Science* **2019**, *365*, 382−386.
(13) (a) Beranek, J.; Hrebabecky, H. *Nucleic Acids Res.* **1976**, *3*, 1387−99. (b) Beranek, J.; Hrebabecky, H. *Nucleic Acid Chem.* **1978**, *1*, 375−379. (c) Sugiura, Y.; Furuya, S.; Furukawa, Y. *Chem. Pharm. Bull.* **1988**, *36*, 3253−3256.
(14) (a) Umemoto, T.; Masada, S.; Miyata, K.; Ogasawara-Shimizu, M.; Murata, S.; Nishi, K.; Ogi, K.; Hayase, Y.; Cho, N. *Tetrahedron* **2017**, *73*, 1211−1218. (b) Sawamoto, H.; Arai, Y.; Yamakoshi, S.; Obika, S.; Kawanishi, E. *Org. Lett.* **2018**, *20*, 1928−1931. (c) Fujisaka, A.; Hari, Y.; Takuma, H.; Rahman, S. M. A.; Yoshikawa, H.; Pang, J.; Imanishi, T.; Obika, S. *Bioorg. Med. Chem.* **2019**, *27*, 1728−1741.
(15) Lin, T.-S.; Luo, M.-Z.; Liu, M.-C.; Zhu, Y.-L.; Gullen, E.; Dutschman, G. E.; Cheng, Y.-C. *J. Med. Chem.* **1996**, *39*, 1757−1759.
(16) (a) Evans, R. K.; Haley, B. E. *Biochemistry* **1987**, *26*, 269−276. (b) Kovaliov, M.; Weitman, M.; Major, D. T.; Fischer, B. *J. Org. Chem.* **2014**, *79*, 7051−7062.
(17) (a) Giziewicz, J.; Wnuk, S. F.; Robins, M. J. *J. Org. Chem.* **1999**, *64*, 2149−2151. (b) Hilko, D. H.; Bornaghi, L. F.; Poulsen, S.-A. *J. Org. Chem.* **2018**, *83*, 11944−11955.
(18) Breugst, M.; Corral Bautista, F.; Mayr, H. *Chem. - Eur. J.* **2012**, *18*, 127−137.
(19) Elgemeie, G. H.; Mohamed, R. A. *J. Carbohydr. Chem.* **2019**, *38*, 20−66.
(20) Zhang, H. W.; Detorio, M.; Herman, B. D.; Solomon, S.; Bassit, L.; Nettles, J. H.; Obikhod, A.; Tao, S.; Mellors, J. W.; Sluis-Cremer, N.; Coats, S. J.; Schinazi, R. F. *Eur. J. Med. Chem.* **2011**, *46*, 3832−3844.
(21) (a) Asakura, J.; Robins, M. J. *J. Org. Chem.* **1990**, *55*, 4928−33. (b) Rayala, R.; Wnuk, S. F. *Tetrahedron Lett.* **2012**, *53*, 3333−3336.
(22) Jones, A. S.; Slater, M. J.; Walker, R. T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1325−1329.
(23) (a) Nussbaumer, F.; Juen, M. A.; Gasser, C.; Kremser, J.; Muller, T.; Tollinger, M.; Kreutz, C. *Nucleic Acids Res.* **2017**, *45*, 9178−9192. (b) Abad, J.-L.; Gaffney, B. L.; Jones, R. A. *J. Org. Chem.* **1999**, *64*, 6575−6582. (c) Shallop, A. J.; Gaffney, B. L.; Jones, R. A. *J. Org. Chem.* **2003**, *68*, 8657−8661.
(24) (a) Tranova, L.; Bucek, J.; Zatloukal, M.; Cankar, P.; Styskala, J. *J. Labelled Compd. Radiopharm.* **2019**, *62*, 118−125. (b) Ariza, X.; Vilarrasa, J. *J. Org. Chem.* **2000**, *65*, 2827−2829. (c) Palazzolo, A.; Feuillastre, S.; Pfeifer, V.; Garcia-Argote, S.; Bouzouita, D.; Tricard, S.; Chollet, C.; Marcon, E.; Buisson, D.-A.; Cholet, S.; Fenaille, F.; Lippens, G.; Chaudret, B.; Pieters, G. *Angew. Chem., Int. Ed.* **2019**, *58*, 4891−4895.
(25) Hatano, A.; Shiraishi, M.; Terado, N.; Tanabe, A.; Fukuda, K. *Bioorg. Med. Chem.* **2015**, *23*, 6683−6688.
(26) Fu, L.; Amato, N. J.; Wang, P.; McGowan, S. J.; Niedernhofer, L. J.; Wang, Y. *Anal. Chem.* **2015**, *87*, 7653−7659.

https://dx.doi.org/10.1021/acs.orglett.0c01941
Org. Lett. XXXX, XXX, XXX−XXX