10-12-2020

Chemical Synthesis of Homogeneous Human E-Cadherin N-Linked Glycopeptides: Stereoselective Convergent Glycosylation and Chemoselective Solid-Phase Aspartylation

Chen Zeng

Bin Sun

Xuefeng Cao

Joshua Zhu

Olawale Micheal Oluwadahunsi

See next page for additional authors

Chemical Synthesis of Homogeneous Human E-Cadherin N-Linked Glycopeptides: Stereoselective Convergent Glycosylation and Chemoselective Solid-Phase Aspartylation

Abstract

We report herein an efficient chemical synthesis of homogeneous human E-cadherin N-linked glycopeptides consisting of a heptapeptide sequence adjacent to the Asn-633 N-glycosylation site with representative N-glycan structures, including a conserved trisaccharide, a core-fucosylated tetrasaccharide, and a complex-type biantennary octasaccharide. The key steps are a chemoselective on-resin aspartylation using a pseudoproline-containing peptide and stereoselective glycosylation using glycosyl fluororide as a donor. This synthetic strategy demonstrates potential utility in accessing a wide range of homogeneous N-linked glycopeptides for the examination of their biological function.

Keywords

anions, peptides and proteins, monomers, free radicals, post-translational modification

Disciplines

Organic Chemistry

Comments

Online access: https://pubs.acs.org/doi/pdf/10.1021/acs.orglett.0c02971

Authors

Chen Zeng, Bin Sun, Xuefeng Cao, Joshua Zhu, Olawale Micheal Oluwadahunsi, Ding Liu, He Zhu, Jiabin Zhang, Qing Zhang, Gaolan Zhang, Christopher Andrew Gibbons, Yunpeng Liu, Jun Zhou, and Peng George Wang

OL Organic Letters

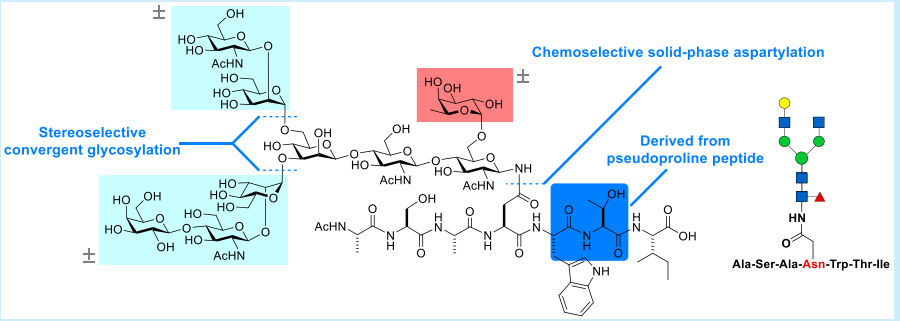
pubs.acs.org/OrgLett Letter

Chemical Synthesis of Homogeneous Human E-Cadherin N-Linked Glycopeptides: Stereoselective Convergent Glycosylation and Chemoselective Solid-Phase Aspartylation

Chen Zeng,[‖] Bin Sun,[‖] Xuefeng Cao, Hailiang Zhu, Olawale Micheal Oluwadahunsi, Ding Liu, He Zhu, Jiabin Zhang, Qing Zhang, Gaolan Zhang, Christopher Andrew Gibbons, Yunpeng Liu, Jun Zhou,* and Peng George Wang*

Cite This: *Org. Lett.* 2020, 22, 8349–8353 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: We report herein an efficient chemical synthesis of homogeneous human E-cadherin N-linked glycopeptides consisting of a heptapeptide sequence adjacent to the Asn-633 N-glycosylation site with representative N-glycan structures, including a conserved trisaccharide, a core-fucosylated tetrasaccharide, and a complex-type biantennary octasaccharide. The key steps are a chemoselective on-resin aspartylation using a pseudoproline-containing peptide and stereoselective glycosylation using glycosyl fluororide as a donor. This synthetic strategy demonstrates potential utility in accessing a wide range of homogeneous N-linked glycopeptides for the examination of their biological function.

E-Cadherin is an N-glycoprotein cell−cell adhesion receptor that is critical in epithelial tissue formation, cell polarity, and differentiation.[1] E-Cadherin mediates cell−cell adhesion via the assembly of multiprotein complexes linked to the actin cytoskeleton.[2] In addition to phosphorylation[3] and O-glycosylation,[4] E-cadherin can be N-glycosylated by high-mannose, hybrid, and complex N-glycans. Human E-cadherins have four potential N-glycosylation sites at residues Asn-554, -566, -618, and -633 in the EC4 and EC5 domains (Figure 1a). During tumor development and progression, the quantitative and qualitative changes in N-glycosylations affect the stability, trafficking, and thus cell adhesion properties of E-cadherin.[5] Importantly, different glycoforms of E-cadherins are promising cancer biomarkers, with potential clinical application to improve the management of patients, and are targets for the development of new therapies. The biological studies of N-glycosylation of E-cadherins often require well-defined N-glycopeptides, which however are difficult to acquire from natural sources due to their microheterogeneity. The developed chemical and enzymatic synthesis strategies, along with native chemical ligation (NCL), enabled the synthesis of complex N-glycopeptides and N-glycoproteins with significant biological importance.[6−10] However, those methods still suffer from poor stereoselective control and low efficiency.[11]

We report herein an efficient chemical synthesis of human E-cadherin N-linked glycopeptides consisting of a heptapeptide sequence adjacent to the N-glycosylation site on Asn-633 with representative N-glycan structures, including a conserved trisaccharide (**1**), a core-fucosylated tetrasaccharide (**2**), and a complex-type biantennary octasaccharide (**3**). As for the efficient formation of a glycopeptide linkage, we developed a chemoselective on-resin aspartylation that relies on the coupling between glycosyl amine **5**, **6**, or **7** (Figure 1b) and pseudoproline-containing peptide **4** on a solid-phase support, which has been proven to suppress the formation of aspartimide. In the efforts to synthesize complex N-glycan structures, different strategies have been developed by several

Received: September 7, 2020
Published: October 12, 2020

https://dx.doi.org/10.1021/acs.orglett.0c02971
Org. Lett. 2020, 22, 8349–8353

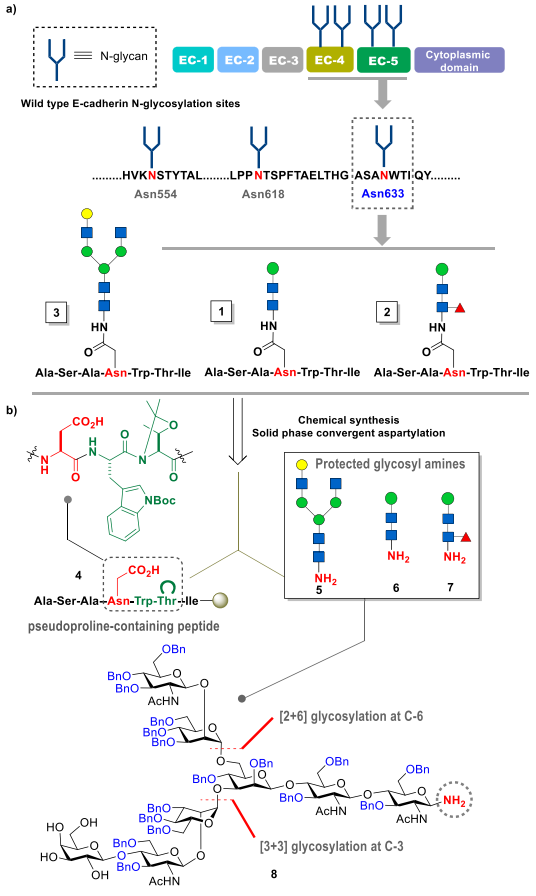


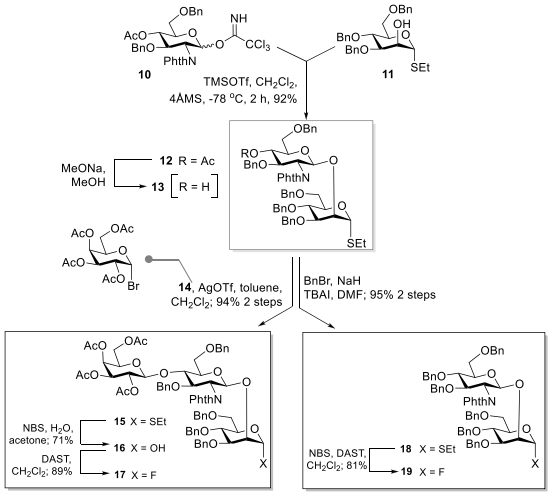
Figure 1. (a) Structural illustration of E-cadherin N-glycosylation sites and target molecules. (b) Synthetic strategy.

research groups.[12] Considering the synthetic efficiency, we envisioned protected biantennary octasaccharide **8** could be assembled by successive coupling of trisaccharyl and disaccharyl donors, either thioglycoside or glycosyl fluorides, onto the 3- and 6-OH positions of the core trisaccharide by stereoselective convergent glycosylations.[13−16]

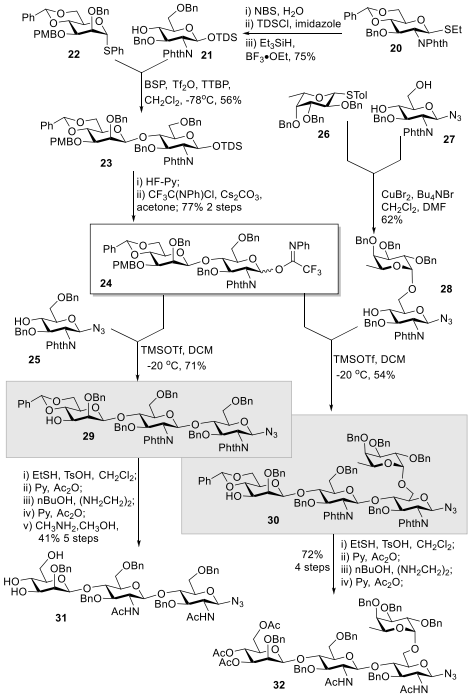
Thus, all tri- and disaccharyl donors for the installation of branch moieties, including **15** and **17**−**19**, can be synthesized in a unified manner from reported building blocks (Scheme 1).[13] In detail, the glycosylation coupling of trichloroacetimidate donor **10** with acceptor **11** under the activation of TMSOTf in CH_2Cl_2 at −78 °C afforded disaccharide **12** in 92% yield. The 4-OAc group was removed by the treatment of $NaOCH_3$ in CH_3OH to provide **13**. Glycosylation of **13** with galactosyl bromide donor **14** under the activation of AgOTf gave trisaccharide **15**. Disaccharide **18** was synthesized by 4-O-benzylation of **13**. Then, glycosides **15** and **18** were subjected to oxidative hydrolysis with NBS followed by treatment with DAST in CH_2Cl_2 to afford glycosyl fluorides **17** and **19**, respectively.

Next, protected core trisaccharide **29** and core-fucosylated tetrasaccharide **30** were readily prepared from the common β-linked disaccharyl donor **24** in a convergent [2+1] and [2+2] manner, respectively (Scheme 2). Acceptor **21** was synthesized from known intermediate **20** in three steps. Then using Crich's stereoselective β-mannosylation approach,[17,18] mannosyl thioglycoside **22** was coupled with **21** to provide **23**, of which the anomeric TDS protection was removed by HF-Py, and the resulting hemiacetal was treated with $CF_3C(NPh)Cl$ to afford

Scheme 1. Synthesis of Di- and Trisaccharide Building Blocks



Scheme 2. Synthesis of the Core Trisaccharide and Tetrasaccharide

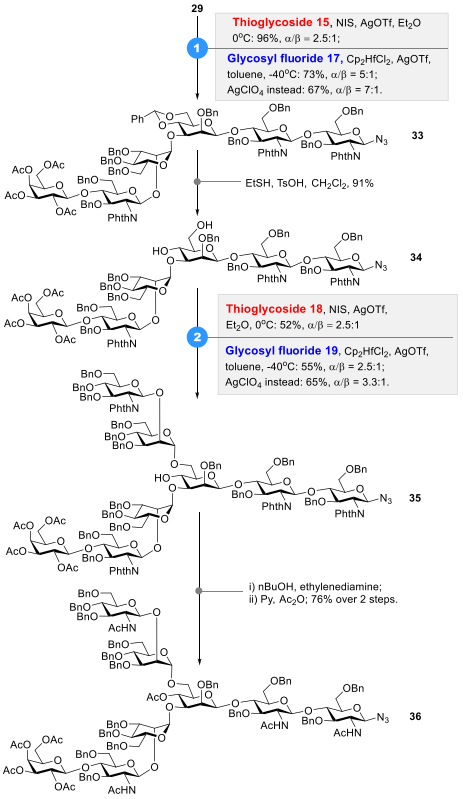


N-phenyl trifluoroacetimidate donor **24**. As an acceptor for the assembly of core-fucosylated tetrasaccharide **30**, disaccharide **28** was synthesized by the regioselective glycosylation at 6-OH of acceptor **27** with fucosyl thioglycoside **26** in the presence of $CuBr_2$ and Bu_4NBr. Then, common disaccharyl donor **24** was coupled with acceptor **25** or **28** by treatment with TMSOTf to provide core trisaccharide **29** or core-fucosylated tetrasaccharide **30**, respectively, each of which was subjected to further protecting group manipulations to give **31** or **32**, respectively.

With all synthetic modules in hand, the assembly of biantennary octasaccharide **36** was investigated, commencing from the 3-O-glycosylation of core trisaccharide **29** with trisaccharyl thioglycoside donor **15** (Scheme 3). The coupling was performed under the activation of NIS/AgOTf in Et_2O at 0 °C, providing the desired α-configured hexasaccharide **33** in

https://dx.doi.org/10.1021/acs.orglett.0c02971
Org. Lett. 2020, 22, 8349−8353

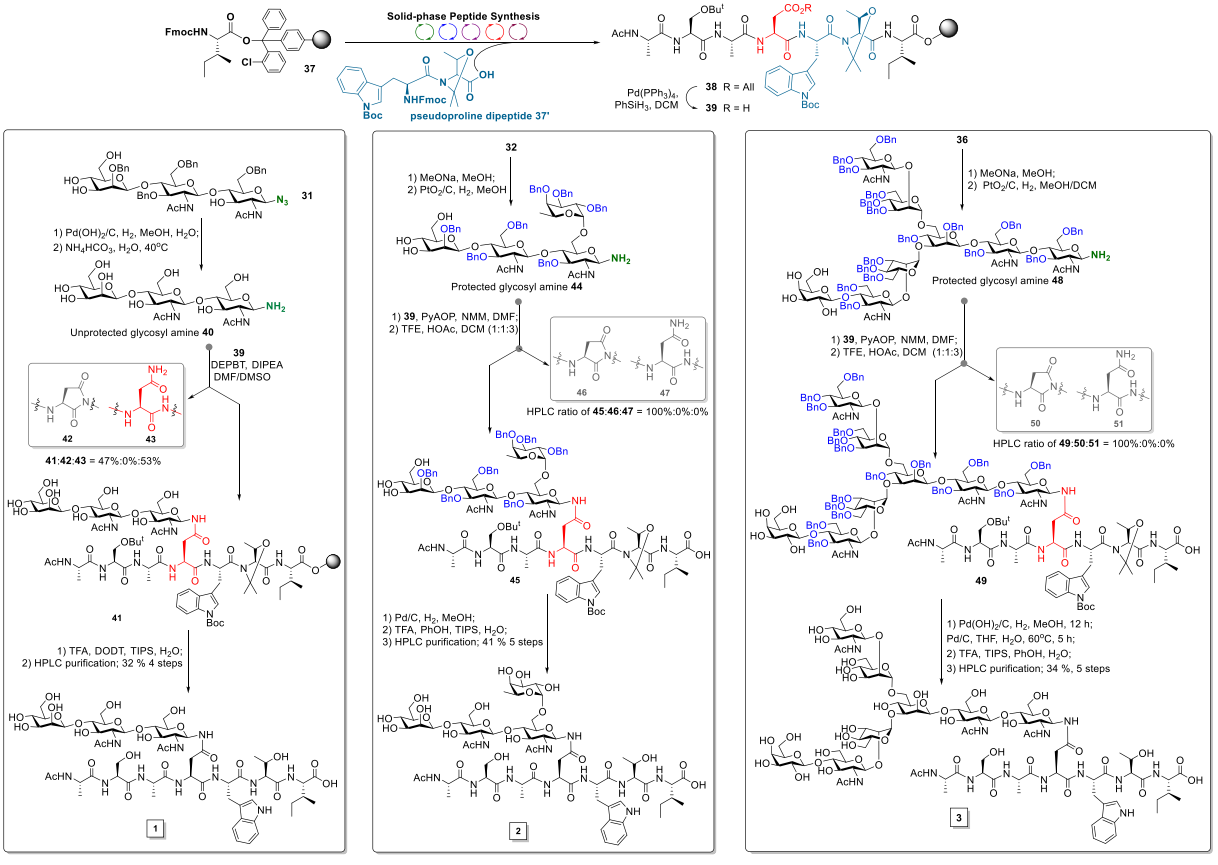
Scheme 3. Synthesis of Octasaccharide 36



96% yield with poor stereoselectivity (2.5:1 α:β ratio).[17,19] Then, we turned to the use of glycosyl fluoride and the coupling of trisaccharyl fluoride **17** with **29** proceeded in the presence of Cp_2HfCl_2/AgOTf in toluene at −40 °C to give hexasaccharide **33** in 73% yield with an improved selectivity (5:1 α:β ratio). When AgOTf was replaced with $AgClO_4$, the stereoselectivity was enhanced to a ratio of 7:1. Next, the resulting hexasaccharide **33** was deprotected in the presence of TsOH and EtSH, providing diol acceptor **34** in 91% yield.[20] The subsequent regioselective glycosylation at 6-OH was then studied. The use of thioglycoside donor **18** delivered the fully protected biantennary N-glycan **35** in 52% yield with an α:β ratio of 2.5:1. Interestingly, a similar counteranion influence on stereoselectivity was observed in glycosylation of **34** with disaccharyl fluoride **19**, wherein the stereoselectivity was enhanced from 2.5:1 to 3.3:1 (α:β) by changing AgOTf to $AgClO_4$. Intermediate **35** was subjected to further protecting group manipulations to give **36**.

After the synthesis of the N-glycan part, we turned our attention to the peptide segment and subsequent aspartylation coupling (Scheme 4). To prevent the formation of the aspartimide side product, we opted to incorporate a pseudoproline unit at the consensus-sequence Thr residue as used by the groups of Danishefsky and Unverzagt.[21] Thus, we prepared the protected heptapeptides **39** using pseudoproline dipeptide building block **37′** corresponding to a Trp-Thr sequence from preloaded acid-sensitive 2-chlorotrityl resin by Fmoc solid-phase peptide synthesis (SPPS) on an automated synthesizer. After the assembly of resin-bound heptapeptide **38**, $Pd(PPh_3)_4$ was used in the presence of phenylsilane to

Scheme 4. Synthesis of Glycopeptides by On-Resin Aspartylation Using a Pseudoproline Peptide



https://dx.doi.org/10.1021/acs.orglett.0c02971
Org. Lett. 2020, 22, 8349−8353

remove the allyl ester group to provide crude carboxylic acid **39** on the solid phase.

Having peptide acid **39** in hand, we set up to synthesize glycopeptide **1** with a core trisaccharide N-glycan. Pseudoproline-containing peptide **39** on resin was readily coupled with unprotected amine **40**, prepared from **31** by global deprotection and amination with NH_4HCO_3, under Lansbury aspartylation conditions using DEPBT as a coupling reagent.[22] The formation of the desired glycopeptide **41** was accompanied by a large amount of asparagine byproduct **43** with a ratio of 47:53 (**41**:**43**). Subsequent addition of a TFA cocktail (TFA/DODT/TIPS/H_2O) served to remove all protecting groups and release the glycopeptide from the resin, thereby providing the target glycopeptide **1** in 32% yield over four steps.

Despite the successful synthesis of **1**, the observation of asparagine formation prompted us to use partly protected glycosyl as the coupling partner in the synthesis of glycopeptides **2** and **3**. To access the partly protected glycosyl amine **44**, tetrasaccharyl azide **32** was subjected to deprotection of acetyl ester groups to avoid late-stage deacetylation that might complicate the synthesis, followed by rapid reduction of the azido group by hydrogenation under the catalysis of PtO_2 to minimize the potential anomerization at the reducing end. **44** was coupled with pseudoproline-containing peptide **39** on solid phase under PyAOP/NMM conditions in DMF, and the resulting glycopeptide was released from the resin by a cocktail (TFE/HOAc/DCM). As anticipated, the desired glycopeptide **45** was obtained with a trace amount of aspartimide **46** and asparagine **47** side products, which demonstrated the huge advantages of using the pseudoproline-containing peptide and partly protected glycosyl amine in aspartylation coupling. Next, the protected glycopeptide **45** was then subjected to debenzylation by hydrogenolysis under Pd/C in CH_3OH and subsequent global deprotection using a TFA cocktail (TFA/phenol/TIPS/H_2O), giving target glycopeptide **2** in 41% yield over five steps.

Having established the optimal synthetic strategy, we continued the synthesis of glycopeptide **3** bearing a complex-type biantennary octasaccharide. Following the same procedure, the synthesis of octasaccharide glycopeptide **49** proceeded smoothly without the formation of aspartimide **50** and asparagine **51** byproducts. The benzyl groups in **49** were removed by hydrogenolysis under Pd/C in CH_3OH. It is worth noting that debenzylation over Pd/C proceeded with partial over-reduction of indole to indoline as indicated by MALDI-TOF-MS analysis. In addition, the use of a catalytic amount of $Pd(OH)_2$/C instead led to quantitative formation of the indoline derivative. To our delight, the indoline derivative can be readily dehydrogenated by the treatment of Pd/C in THF/H_2O to afford the pure indole derivative. Finally, the deprotection using a TFA lotion (TFA/phenol/TIPS/H_2O) provided the target glycopeptide **3** in 34% yield over five steps. The chemical structures of **1**−**3** were determined on the bass of a combination of two-dimensional NMR techniques.[23,24]

In conclusion, we describe herein an efficient synthesis of homogeneous human E-cadherin N-linked glycopeptides consisting of a heptapeptide sequence adjacent to the Asn-633 N-glycosylation site and representative N-glycan structures, including a conserved trisaccharide, a core-fucosylated tetrasaccharide, and a complex-type biantennary octasaccharide. We developed a chemoselective on-resin aspartylation that relies on the coupling between a partly protected glycosyl amine and a pseudoproline-containing peptide, which have been proven to eliminate the aspartimide and asparagine side products. As for the assembly of the biantennary N-glycan moiety, oligosaccharyl donors were utilized to introduce the C-3/C-6 branches via convergent glycosylations, wherein the stereoselective control was strongly influenced by the glycosyl donor leaving groups (e.g., SEt and F) as well as the solvent and additives. This synthetic strategy demonstrates potential for accessing a wide range of homogeneous N-linked glycopeptides for the study of their biological function.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02971.

Exerimental procedures and spectral data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Peng George Wang − *School of Medicine, Southern University of Science and Technology, Shenzhen 518055, China; Department of Chemistry, Georgia State University, Atlanta, Georgia 30303, United States;* orcid.org/0000-0003-3335-6794; Email: wangp6@sustech.edu.cn

Jun Zhou − *Department of Chemistry, Georgia State University, Atlanta, Georgia 30303, United States; R&D Headquarters, WuXi AppTec, Shanghai 200131, China*; Email: jun.m.zhou@outlook.com

Authors

Chen Zeng − *School of Medicine, Southern University of Science and Technology, Shenzhen 518055, China;* orcid.org/0000-0001-5350-7639

Bin Sun − *School of Medicine, Southern University of Science and Technology, Shenzhen 518055, China*

Xuefeng Cao − *Department of Chemistry, Georgia State University, Atlanta, Georgia 30303, United States*

Hailiang Zhu − *Department of Chemistry, Georgia State University, Atlanta, Georgia 30303, United States*

Olawale Micheal Oluwadahunsi − *Department of Chemistry, Georgia State University, Atlanta, Georgia 30303, United States*

Ding Liu − *Department of Chemistry, Georgia State University, Atlanta, Georgia 30303, United States*

He Zhu − *Department of Chemistry, Georgia State University, Atlanta, Georgia 30303, United States*

Jiabin Zhang − *Department of Chemistry, Georgia State University, Atlanta, Georgia 30303, United States*

Qing Zhang − *Department of Chemistry, Georgia State University, Atlanta, Georgia 30303, United States*

Gaolan Zhang − *Department of Chemistry, Georgia State University, Atlanta, Georgia 30303, United States*

Christopher Andrew Gibbons − *Department of Chemistry, Georgia State University, Atlanta, Georgia 30303, United States*

Yunpeng Liu − *Department of Chemistry, Georgia State University, Atlanta, Georgia 30303, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c02971

Author Contributions

[‖]C.Z. and B.S. contributed equally to this work.

https://dx.doi.org/10.1021/acs.orglett.0c02971
Org. Lett. 2020, 22, 8349−8353

Notes

The authors declare no competing financial interest.

REFERENCES

(1) (a) Song, J.-H.; Huels, D. J.; Ridgway, R. A.; Sansom, O. J.; Kholodenko, B. N.; Kolch, W.; Cho, K.-H. *Cell Rep.* **2014**, *7*, 94−103. (b) Bondow, B. J.; Faber, M. L.; Wojta, K. J.; Walker, E. M.; Battle, M. A. *Dev. Biol.* **2012**, *371*, 1−12. (c) Tan, C. W.; Hirokawa, Y.; Gardiner, B. S.; Smith, D. W.; Burgess, A. W. *PLoS One* **2013**, *8*, No. e78519. (d) Solanas, G.; Cortina, C.; Sevillano, M.; Batlle, E. *Nat. Cell Biol.* **2011**, *13*, 1100−1107. (e) Wang, F.; Scoville, D.; He, X. C.; Mahe, M. M.; Box, A.; Perry, J. M.; Smith, N. R.; Lei, N. Y.; Davies, P. S.; Fuller, M. K.; et al. *Gastroenterology* **2013**, *145*, 383−395.

(2) (a) Takeichi, M. *Curr. Opin. Cell Biol.* **1995**, *7*, 619−627. (b) Nollet, F.; Berx, G.; van Roy, F. *Mol. Cell Biol. Res. Commun.* **1999**, *2*, 77−85. (c) Yap, A. S. *Cancer Invest.* **1998**, *16*, 252−261.

(3) (a) McEwen, A. E.; Maher, M. T.; Mo, R.; Gottardi, C. J. *Mol. Biol. Cell* **2014**, *25*, 2365−2374. (b) Matteucci, E.; Ridolfi, E.; Desiderio, M. A. *Cell. Mol. Life Sci.* **2006**, *63*, 2016−2026.

(4) Carvalho, S.; Oliveira, T.; Bartels, M. F.; Miyoshi, E.; Pierce, M.; Taniguchi, N.; Carneiro, F.; Seruca, R.; Reis, C. A.; Strahl, S.; Pinho, S. S. *Oncotarget* **2016**, *7*, 65231−65246.

(5) (a) Zhao, H.; Liang, Y.; Xu, Z.; Wang, L.; Zhou, F.; Li, Z.; Jin, J.; Yang, Y.; Fang, Z.; Hu, Y.; Zhang, L.; Su, J.; Zha, X. *J. Cell. Biochem.* **2008**, *104*, 162−175. (b) Liwosz, A.; Lei, T.; Kukuruzinska, M. A. *J. Biol. Chem.* **2006**, *281*, 23138−23149. (c) Pinho, S. S.; Osório, H.; Nita-Lazar, M.; Gomes, J.; Lopes, C.; Gärtner, F.; Reis, C. A. *Biochem. Biophys. Res. Commun.* **2009**, *379*, 1091−1096.

(6) Dawson, P. E.; Muir, T. W.; Clark-Lewis, I.; Kent, S. B. *Science* **1994**, *266*, 776−778.

(7) (a) Bohé, L.; Crich, D. *Trends Glycosci. Glycotechnol.* **2010**, *22*, 1−15. (b) Zeng, Y.; Wang, Z.; Whitfield, D.; Huang, X. *J. Org. Chem.* **2008**, *73*, 7952−7962. (c) Fraser-Reid, B.; López, J. C.; Gómez, A. M.; Uriel, C. *Eur. J. Org. Chem.* **2004**, *2004*, 1387−1395.

(8) (a) Hsu, C.-H.; Hung, S.-C.; Wu, C.-Y.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2011**, *50*, 11872−11923. (b) Li, B.; Zeng, Y.; Hauser, S.; Song, H.-J.; Wang, L.-X. *J. Am. Chem. Soc.* **2005**, *127* (27), 9692−9693. (c) Huang, W.; Li, C.-S.; Li, B.; Umekawa, M.; Yamamoto, K.; Zhang, X.-Y.; Wang, L.-X. *J. Am. Chem. Soc.* **2009**, *131* (6), 2214−2223. (d) Kajihara, Y.; Yamamoto, T.; Nagae, H.; Nakashizuka, M.; Sakakibara, T.; Terada, I. *J. Org. Chem.* **1996**, *61*, 8632−8635. (e) Kajihara, Y.; Suzuki, Y.; Yamamoto, N.; Sasaki, K.; Sakakibara, T.; Juneja, L. R. *Chem. - Eur. J.* **2004**, *10*, 971−985.

(9) (a) Boltje, T. J.; Kim, J.-H.; Park, J.; Boons, G.-J. *Nat. Chem.* **2010**, *2*, 552−557. (b) Fang, T.; Mo, K.-F.; Boons, G.-J. *J. Am. Chem. Soc.* **2012**, *134*, 7545−7552. (c) Wang, Z.; Chinoy, Z. S.; Ambre, S. G.; Peng, W.; McBride, R.; de Vries, R. P.; Glushka, J.; Paulson, J. C.; Boons, G. J. *Science* **2013**, *341*, 379−383.

(10) (a) Lee, H.-K.; Scanlan, C. N.; Huang, C.-Y.; Chang, A. Y.; Calarese, D. A.; Dwek, R. A.; Rudd, P. M.; Burton, D. R.; Wilson, I. A.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1000−1003. (b) Mandal, M.; Dudkin, V. Y.; Geng, X.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 2557−2561. (c) Tsai, Y.-H.; Götze, S.; Vilotijevic, I.; Grube, M.; Silva, D. V.; Seeberger, P. H. *Chem. Sci.* **2013**, *4*, 468−481. (d) Du, J. J.; Gao, X. F.; Xin, L. M.; Lei, Z.; Liu, Z.; Guo, J. *Org. Lett.* **2016**, *18*, 4828−4831. (e) Du, J. J.; Zhang, L.; Gao, X. F.; Sun, H.; Guo, J. *Front. Chem.* **2020**, *8*, 396.

(11) (a) Li, Z.; Gildersleeve, J. C. *J. Am. Chem. Soc.* **2006**, *128*, 11612−11619. (b) Christensen, H. M.; Oscarson, S.; Jensen, H. H. *Carbohydr. Res.* **2015**, *408*, 51−95.

(12) (a) Chen, R.; Tolbert, T. J. *J. Am. Chem. Soc.* **2010**, *132*, 3211−3216. (b) Wang, P.; Dong, S.; Shieh, J. H.; Peguero, E.; Hendrickson, R.; Moore, M. A.; Danishefsky, S. J. *Science* **2013**, *342*, 1357−1360. (c) Walczak, M. A.; Hayashida, J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2013**, *135*, 4700−4703. (d) Pratt, M. R.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2003**, *125*, 6149−6159. (e) Mezzato, S.; Unverzagt, C. *Carbohydr. Res.* **2010**, *345*, 1306−1315. (f) Shao, N.; Xue, J.; Guo, Z. *Angew. Chem., Int. Ed.* **2004**, *43*, 1569−1573. (g) Yamamoto, N.; Tanabe, Y.; Okamoto, R.; Dawson, P. E.; Kajihara, Y. *J. Am. Chem. Soc.* **2008**, *130*, 501−510.

(13) (a) Karche, N. P.; Jachak, S. M.; Dhavale, D. D. *J. Org. Chem.* **2003**, *68*, 4531−4534. (b) Volbeda, A. G.; Kistemaker, H. A. V.; Overkleeft, H. S.; van der Marel, G. A.; Filippov, D. V.; Codée, J. D. C. *J. Org. Chem.* **2015**, *80*, 8796−8806. (c) Zhou, J.; Yang, L.; Hu, W. *J. Org. Chem.* **2014**, *79*, 4718−4726. (d) Worm-Leonhard, K.; Larsen, K.; Jensen, K. J. *J. Carbohydr. Chem.* **2007**, *26*, 349−368. (e) Ohara, K.; Lin, C.-C.; Yang, P.-J.; Hung, W.-T.; Yang, W.-B.; Cheng, T. J. R.; Fang, J.-M.; Wong, C.-H. *J. Org. Chem.* **2013**, *78*, 6390−6411.

(14) (a) Patil, P. S.; Cheng, T.-J. R.; Zulueta, M. M. L.; Yang, S.-T.; Lico, L. S.; Hung, S.-C. *Nat. Commun.* **2015**, *6*, 7239. (b) Wu, Z.; Guo, X.; Wang, Q.; Swarts, B. M.; Guo, Z. *J. Am. Chem. Soc.* **2010**, *132*, 1567−1571. (c) Swarts, B. M.; Guo, Z. *J. Am. Chem. Soc.* **2010**, *132*, 6648−6650. (d) Wu, X.; Guo, Z. *Org. Lett.* **2007**, *9*, 4311−4313. (e) Gao, J.; Liao, G.; Wang, L.; Guo, Z. *Org. Lett.* **2014**, *16*, 988−991. (f) Gao, J.; Guo, Z. J. *J. Org. Chem.* **2013**, *78*, 12717−12725.

(15) (a) Ritter, T. K.; Mong, K. K. T.; Liu, H. T.; Nakatani, T.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4657−4660. (b) Lee, J.-C.; Greenberg, W. A.; Wong, C.-H. *Nat. Protoc.* **2006**, *1*, 3143−3152.

(16) (a) Tsai, Y.-H.; Götze, S.; Azzouz, N.; Hahm, H. S.; Seeberger, P. H.; Varon Silva, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 9961−9964. (b) Liu, X.; Kwon, Y. U.; Seeberger, P. H. *J. Am. Chem. Soc.* **2005**, *127*, 5004−5005. (c) Liu, X.; Stocker, B. L.; Seeberger, P. H. *J. Am. Chem. Soc.* **2006**, *128*, 3638−3648. (d) Hölemann, A.; Stocker, B. L.; Seeberger, P. H. *J. Org. Chem.* **2006**, *71*, 8071−8088. (e) Seeberger, P. H.; Soucy, R. L.; Kwon, Y. U.; Snyder, D. A.; Kanemitsu, T. *Chem. Commun.* **2004**, 1706−1707. (f) Xue, J.; Guo, Z. *J. Am. Chem. Soc.* **2003**, *125*, 16334−16339.

(17) (a) Crich, D.; Cai, W. *J. Org. Chem.* **1999**, *64*, 4926−4930. (b) Crich, D.; Vinogradova, O. *J. Org. Chem.* **2006**, *71*, 8473−8480. (c) Crich, D.; Li, L. *J. Org. Chem.* **2007**, *72*, 1681−1690. (d) Crich, D. *J. Org. Chem.* **2011**, *76*, 9193−9209.

(18) (a) Hashimoto, Y.; Tanikawa, S.; Saito, R.; Sasaki, K. *J. Am. Chem. Soc.* **2016**, *138*, 14840−14843. (b) Codée, J. D. C.; van den Bos, L. J.; de Jong, A.-R.; Dinkelaar, J.; Lodder, G.; Overkleeft, H. S.; van der Marel, G. A. *J. Org. Chem.* **2009**, *74*, 38−47. (c) Dinkelaar, J.; de Jong, A. R.; van Meer, R.; Somers, M.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *J. Org. Chem.* **2009**, *74*, 4982−4991. (d) Hosoya, T.; Kosma, P.; Rosenau, T. *Carbohydr. Res.* **2015**, *401*, 127−131.

(19) Kartha, K. P. R.; Cura, P.; Aloui, M.; Readman, S. K.; Rutherford, T. J.; Field, R. A. *Tetrahedron: Asymmetry* **2000**, *11*, 581−593.

(20) Aly, M. R.; Rochaix, P.; Amessou, M.; Johannes, L.; Florent, J. C. *Carbohydr. Res.* **2006**, *341*, 2026−2036.

(21) (a) Wang, P.; Aussedat, B.; Vohra, Y.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 11571−11575. (b) Mönnich, M.; Eller, S.; Karagiannis, T.; Perkams, L.; Luber, T.; Ott, D.; Niemietz, M.; Hoffman, J.; Walcher, J.; Berger, L.; et al. *Angew. Chem., Int. Ed.* **2016**, *55*, 10487−10492. (c) Ullmann, V.; Rädisch, M.; Boos, I.; Freund, J.; Pöhner, C.; Schwarzinger, S.; Unverzagt, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 11566−11570.

(22) (a) Anisfeld, S. T.; Lansbury, P. T. *J. Org. Chem.* **1990**, *55*, 5560−5562. (b) Cohen-Anisfeld, S. T.; Lansbury, P. T. *J. Am. Chem. Soc.* **1993**, *115*, 10531−10537.

(23) (a) Duus, J. Ø.; Gotfredsen, C. H.; Bock, K. *Chem. Rev.* **2000**, *100*, 4589−4614. (b) Breton, R. C.; Reynolds, W. F. *Nat. Prod. Rep.* **2013**, *30*, 501−524.

(24) (a) Kozminski, W.; Nanz, D. *J. Magn. Reson.* **1997**, *124*, 383−392. (b) Kozminski, W.; Nanz, D. *J. Magn. Reson.* **2000**, *142*, 294−299. (c) Palermo, G.; Riccio, R.; Bifulco, G. *J. Org. Chem.* **2010**, *75*, 1982−1991. (d) Nilewski, C.; Geisser, R. W.; Ebert, M.-O.; Carreira, E. *J. Am. Chem. Soc.* **2009**, *131*, 15866−15876. (e) Morinaka, B. I.; Molinski, T. F. *Org. Lett.* **2011**, *13*, 6338−6341.

https://dx.doi.org/10.1021/acs.orglett.0c02971
Org. Lett. 2020, 22, 8349−8353