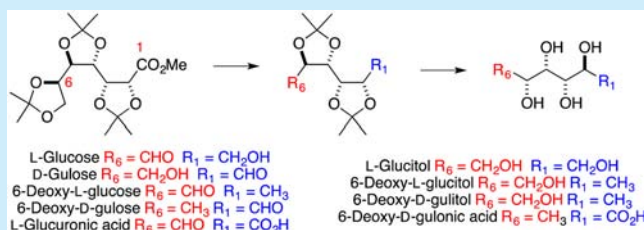


Triacetone of Glucoheptonic Acid in the Scalable Syntheses of D-Gulose, 6-Deoxy-D-gulose, L-Glucose, 6-Deoxy-L-glucose, and Related Sugars

Zilei Liu,^{†,§} Akihito Yoshihara,^{*,‡} Sarah F. Jenkinson,[†] Mark R. Wormald,[§] Ramón J. Estévez,^{||} George W. J. Fleet,^{*,†} and Ken Izumori[‡][†]Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Oxford OX1 3TA, U.K.[‡]International Institute of Rare Sugar Research and Education, Kagawa University, Miki, Kagawa 761-0795, Japan[§]Oxford Glycobiology Institute, Department of Biochemistry, University of Oxford, Oxford OX1 3QU, U.K.^{||}Departamento de Química Orgánica and Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain

Supporting Information

ABSTRACT: Ease of separation of petrol-soluble acetonides derived from the triacetone of methyl glucoheptonate allows scalable syntheses of rare sugars containing the L-gluco or D-gulo structural motif with any oxidation level at the C6 or C1 position of the hexose, usually without chromatography: *meso*-D-glycero-D-guloheptitol available in two steps is an ideal entry point for the study of the biotechnological production of heptoses.



Sodium glucoheptonate **1** (>98% pure, prepared from the Kiliani reaction of sodium cyanide with glucose,¹ is one of the cheapest bulk carbohydrates available. On a 100 g scale, **1** may be converted in a morning to the pure triacetone methyl ester **2** by a procedure that involves extraction of the crude product with cyclohexane as the only purification step (Scheme 1). The value of **2** in the preparation of rare sugars has been demonstrated by large-scale syntheses of L-glucose **4** and L-glucuronic acid **6**: selective deprotection of the terminal acetonide in **2**, followed by LiAlH_4 reduction of **2a**, and periodate cleavage gave aldehyde **3**; acid hydrolysis of **3** gave L-glucose **4** in 80% yield from the triacetone with purification only by solvent extraction and crystallization.² Partial hydrolysis of **2** and subsequent oxidation with periodate afforded the stable aldehyde **5**, which with trifluoroacetic acid hydrolysis gave L-glucuronic acid **6**, isolated as the crystalline lactone in 78% yield from **2**.² This paper describes the synthesis of a wide range of rare sugars via intermediate acetonides derived from **2**, all easily accessible in multigram quantities with any oxidation level at C1 or C6 of the sugar.

For the synthesis of D-gulose **9**, treatment of **5** on a multigram scale with sodium borohydride in methanol at 0 °C gave completely regioselective reduction of the aldehyde to provide alcohol **7** (96%); there was no reduction of the ester group (Scheme 1). Further reduction with DIBAL-H afforded the D-gulose derivative **8** with C1 and C6 unprotected (86%). One-step DIBAL-H reduction of **5** directly to **8** did not give a clean product. Removal of the acetonides in **8** by acid ion-exchange resin gave D-gulose **9**³ in quantitative yield (71% from triacetone **2**). Simultaneous reduction of both the aldehyde

and ester groups in **5** by LiAlH_4 formed the diol **10** (90%), which on treatment with acid ion-exchange resin gave L-glucitol **11** (100%) in 77% yield from the triacetone **2**. Alditols are ideal substrates for biotechnological conversion to rare sugars: microbial oxidation of L-glucitol **11** gave D-sorbose⁴ **12** in 90% yield.⁵ ^{13}C and ^1H NMR spectra of D-gulose **9** and L-glucitol **11** were identical to those of authentic samples (see Supporting Information).

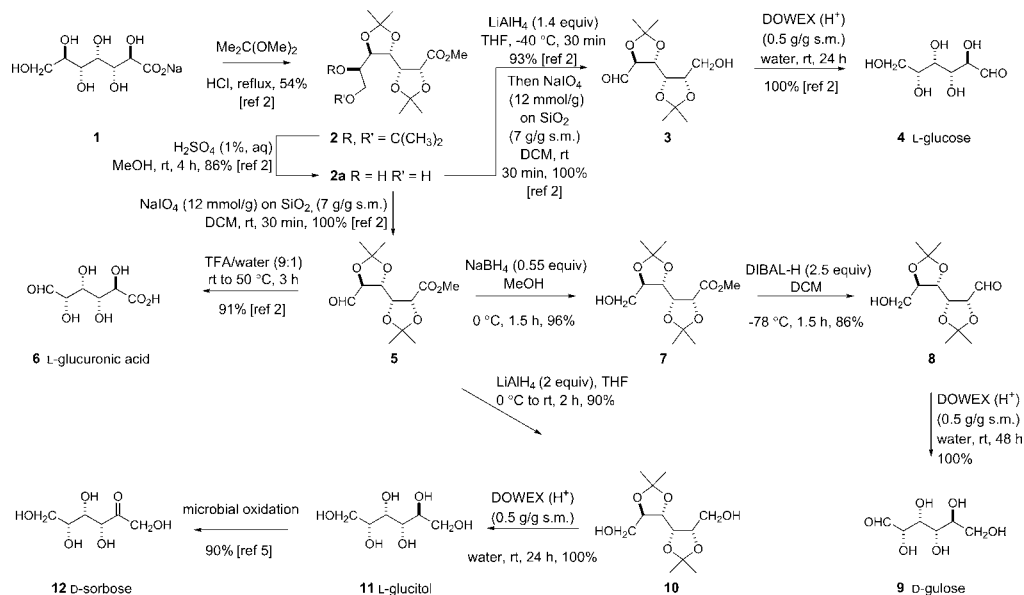
Acetonide **2** or **7** can be used for efficient syntheses of 6-deoxy sugars. Derivatives of 6-deoxy-D-gulose can be efficiently accessed by initial deoxygenation of the primary alcohol in **7** (Scheme 2). Esterification of **7** with triflic anhydride in the presence of pyridine, followed by nucleophilic substitution with sodium iodide in butanone, gave iodide **13** (81% over two steps). Hydrogenation of **13** in methanol in the presence of palladium on charcoal and triethylamine gave the crystalline diacetone **14**, which was deprotected to afford 6-deoxy-D-gulonolactone **15**⁶ (100%). Synthesis of the crystalline lactone **15** from the triacetone **2** in 61% yield required no chromatography; the route is far more convenient than procedures from L-rhamnose⁷ or D-gulonolactone.⁸

Reduction of ester **14** with DIBAL-H at -78 °C gave the protected aldehyde **17** (84%) and a small amount of the alcohol **16** (14%), easily separated by flash chromatography. Acid ion-exchange hydrolysis of the acetonides in **17** formed 6-deoxy-D-gulose **18**⁹ (100%), identical to a sample from L-rhamnose⁷

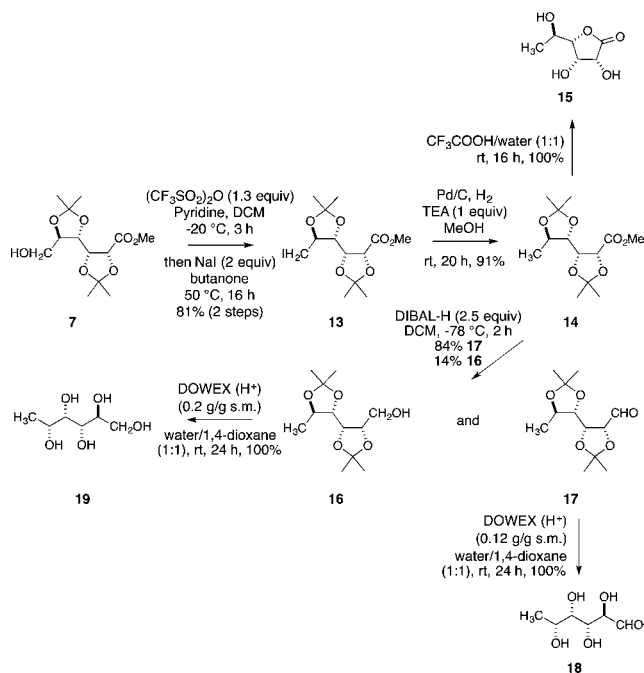
Received: July 13, 2016

Published: August 3, 2016

Scheme 1. L-Glucose 4, D-Gulose 8, and L-Glucitol 11



Scheme 2. 6-Deoxy-D-gulonolactone 15, 6-Deoxy-D-gulose 18, and 6-Deoxy-D-glucitol [6-Deoxy-D-glucitol] 19



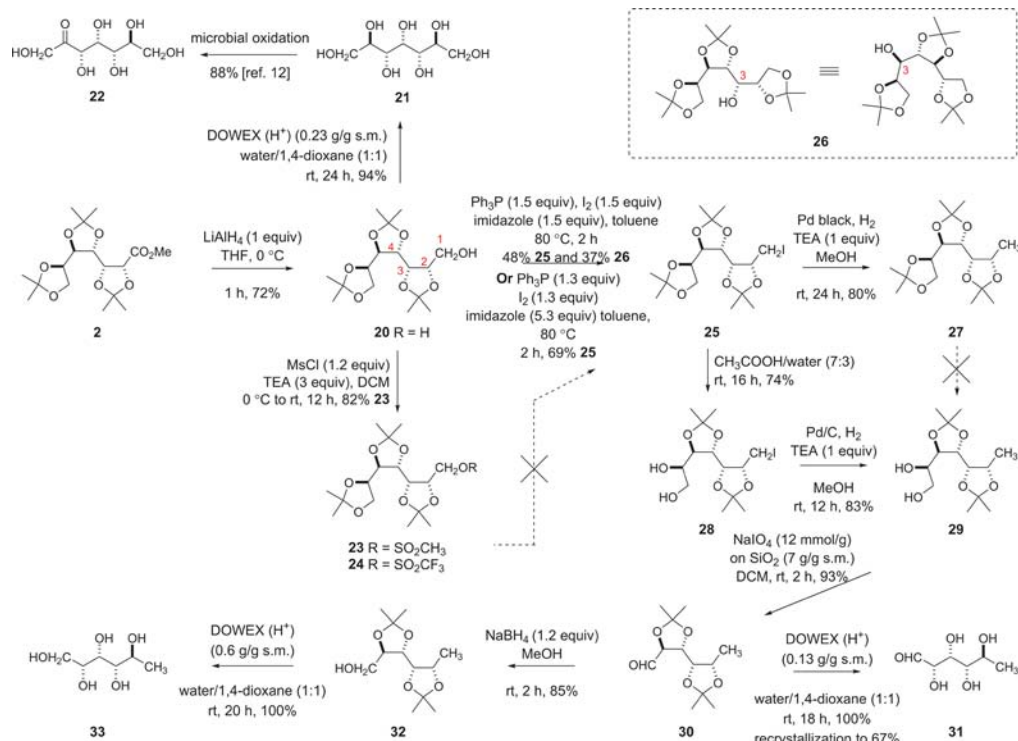
(overall 56% yield from 2). Acid hydrolysis of 16 gave 6-deoxy-D-gulitol (1-deoxy-L-glucitol) 19.¹⁰

Heptitol¹¹ triacetone 20 was formed in the reduction of methyl ester 2 with LiAlH₄ (74%) (Scheme 3). Acid ion-exchange hydrolysis of 20 formed the *meso*-heptitol 21 (94%). Microbial oxidation of 21 with *Acetobacter suboxydans* forms L-glucoheptulose 22 in 88% yield, as described long ago by Hudson,¹² and provides an ideal entry point for the isomerization of seven carbon sugars by the biotechnology of Izumori;¹³ there is much current interest in the investigation of the synthesis and biological properties of heptuloses.¹⁴

Deoxygenation of the primary alcohol in triacetone 20 gave efficient syntheses of 6-deoxy-L-glucose (L-quinovose) derivatives. Triflate ester 24 derived from 20 was unstable, and it was

not possible to convert 2 to the corresponding iodide 25 by an analogous protocol used for 7 to 13. Reaction of 20 with mesyl chloride and triethylamine in DCM gave mesylate 23 (82%); all attempts at nucleophilic displacement of the primary mesylate in 23 failed: 23 was recovered unchanged on heating overnight with sodium iodide in acetone at reflux or in DMF at 100 °C; reduction of 23 with LiAlH₄ resulted in nucleophilic attack on sulfur (rather than carbon) to give 20. Although S_N reactions in carbohydrate chemistry are difficult due to the presence of β-oxygen substituents,¹⁵ iodides are almost always formed in good yields by displacement of primary mesylates. Additional steric hindrance to nucleophilic attack may be due to the *cis* relationship in the C2–C3 ketal between the ketal at C4–C5 and the leaving group at C1. This would also explain the instability of triflate 24 because the ketal oxygen at C4 might act as an internal nucleophile on the leaving group at C1. For the introduction of an iodide at C1, it is necessary to have the iodide present during the activation of the leaving group at C1. Appel reaction¹⁶ of alcohol 20 with imidazole/triphenylphosphine/iodine in a 1:1:1 ratio gave iodide 25 (48%) together with another acetone 26 (37%). The structure of 26 was confirmed by NMR spectra with CDCl₃ as solvent: (i) three quaternary carbon signals (δ = 109.3, 109.7, 109.8 ppm) indicated the presence of three five-membered-ring ketals; (ii) the peak of free hydroxyl group (δ = 2.17 ppm) of 26 was a doublet in ¹H NMR spectrum; (iii) ¹H–¹H correlation spectroscopy indicated the hydroxyl group is correlated with H-3. Formation of 26 was also observed by leaving 20 in CDCl₃ for 3 weeks at room temperature. 20 and 26 are the only two possible triacetones of heptitol 21 with only five-ring ketals. Formation of 26 from 20 is acid-catalyzed. Accordingly, when the Appel reactant ratio of imidazole/triphenylphosphine/iodine was changed to a 4:1:1 with an excess of base, conversion of alcohol 20 gave iodide 25 in 69% yield on an 11 g scale without the formation of 26.

Hydrogenolysis of iodide 25 with palladium black and triethylamine gave the methyl triacetone 27 (80%). However, no conditions for selective acid hydrolysis of 27 to the diol 29 were found. In contrast, the iodomethyl triacetone 25 with aqueous acetic acid gave diol 28 (74%). Hydrogenolysis of 28 in methanol in the presence of palladium on charcoal and

Scheme 3. *meso*-D-Glycero-D-guloheptitol 21, 6-Deoxy-L-glucose [L-Quinovose] 31, and 6-Deoxy-L-glucitol 33

triethylamine afforded the crystalline deoxyheptitol diacetone 29 (83%). Cleavage of diol 29 with sodium periodate on silica gel in DCM¹⁷ formed aldehyde 30 (93%), which on acid ion-exchange resin hydrolysis gave deoxyhexose 31 (67%), identical to a sample produced from L-rhamnose.⁷ Reduction of aldehyde 30 by sodium borohydride in methanol gave diacetone 32 (85%), which on removal of the acetonide protecting groups by acid hydrolysis formed 6-deoxyalditol 33 (100%). 6-Deoxy-L-glucose 31 and 6-deoxy-L-glucitol 33 were formed in overall yields of 19 and 24%, respectively, from the heptonate triacetone 2 without the need for any chromatography. The NMR spectra of 6-deoxy-L-glucose were identical to those of commercially available 6-deoxy-D-glucose.

Heptonic acid lactones with only acetonide protection derived from Kiliani synthesis on aldoses¹⁸ or ketoses¹⁹ are well-established intermediates for the efficient synthesis of highly functionalized targets.²⁰ This paper underlines the value of triacetones²¹ derived from seven carbon sugars; 2 is a divergent intermediate for access to rare sugars possessing either a D-gulo or L-gluco structural motif with any oxidation level at C1 or C6. This approach, which may be general for heptonates, increases chemical and biotechnological procedures for easy access to rare sugars.²² L-Rhamnose, a cheap 6-deoxyhexose, provides an alternative strategy for the synthesis of many of its diastereomers and derivatives.^{7,23} In particular, microbial oxidations of alditols to ketoses usually give high-yield regioselective reactions to a pure ketose; 6-deoxyalditols 19 and 33 are useful starting materials for the biotechnology of Izumori in the synthesis of deoxyhexoses.²⁴

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02041.

Experimental procedures and full spectroscopic data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: yoshihara@ag.kagawa-u.ac.jp.

*E-mail: george.fleet@chem.ox.ac.uk.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Leverhulme Trust (G.W.J.F.) and Xunta de Galicia (Project GRC2014/040). We are grateful to Carbosynth for samples of authentic sugars for comparison purposes.

■ REFERENCES

- (1) Quotes at <\$10 per kilogram from reputable companies on alibaba.com on 07/08/16.
- (2) Martínez, R. F.; Liu, Z.; Glawar, A. F. G.; Yoshihara, A.; Izumori, K.; Fleet, G. W. J.; Jenkinson, S. F. *Angew. Chem., Int. Ed.* **2014**, *53*, 1160–1162.
- (3) Morimoto, K.; Shimonishi, T.; Miyake, S.; Takata, G.; Izumori, K. *Biosci., Biotechnol., Biochem.* **2013**, *77*, 253–258.
- (4) (a) Li, Z.; He, B.; Gao, Y.; Cai, L. *J. Carbohydr. Chem.* **2015**, *34*, 349–357. (b) Dhawale, M. R.; Szarek, W. A.; Hay, G. W.; Kropinski, A. M. B. *Carbohydr. Res.* **1986**, *155*, 262–265. (c) Khan, A.; Takahata, S.; Okaya, H.; Tsumura, T. *J. Ferment. Bioeng.* **1992**, *74*, 149–152.
- (5) Gauer, S.; Wang, Z. J.; Otten, H.; Etienne, M.; Bjerrum, M. J.; Lo Leggio, L.; Walcarus, A.; Giffhorn, F.; Kohring, G. W. *Appl. Microbiol. Biotechnol.* **2014**, *98*, 3023–3032.
- (6) Levene, P. A.; Compton, J. J. *Biol. Chem.* **1935**, *111*, 335–46.
- (7) Liu, Z.; Yoshihara, A.; Kelly, C.; Heap, J.; Marqvorsen, M. H. S.; Jenkinson, S. F.; Wormald, M. R.; Otero, J. M.; Estévez, A.; Kato, A.

Fleet, G. W. J.; Estévez, R. J.; Izumori, K. *Chem. - Eur. J.* **2016**, DOI: [10.1002/chem.201602482](https://doi.org/10.1002/chem.201602482).

(8) (a) Fairbanks, A. J.; Carpenter, N. C.; Fleet, G. W. J.; Ramsden, N. G.; Cenci de Bello, I.; Winchester, B.; Al-Daher, S. S.; Nagahashi, G. *Tetrahedron* **1992**, *48*, 3365–3376. (b) Davis, B. G.; Hull, A.; Smith, C.; Nash, R. J.; Watson, A. A.; Winkler, D. A.; Griffiths, R. C.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2947–2960.

(9) Kaufmann, H. *Helv. Chim. Acta* **1965**, *48*, 769–79.

(10) Bukhari, M. A.; Foster, A. B.; Lehmann, J.; Webber, J. M. *J. Chem. Soc.* **1963**, 2287–2290.

(11) (a) Gardner, P. M.; Winzer, K.; Davis, B. G. *Nat. Chem.* **2009**, *1*, 377–383. (b) Angyal, S. J.; Le Fur, R. *Carbohydr. Res.* **1984**, *126*, 15–26. (c) Pratt, J. W.; Richtmyer, N. K.; Hudson, C. S. *J. Am. Chem. Soc.* **1952**, *74*, 2210–2214.

(12) Maclay, W. D.; Hann, R. M.; Hudson, C. S. *J. Am. Chem. Soc.* **1942**, *64*, 1606–1609.

(13) (a) Izumori, K. *J. Biotechnol.* **2006**, *124*, 717–722. (b) Chen, Z.; Zhang, W.; Zhang, T.; Jiang, B.; Mu, W. *Appl. Microbiol. Biotechnol.* **2016**, *100*, 6971–6979. (c) Li, Z.; Gao, Y.; Nakanishi, H.; Gao, X.; Cai, L. *Beilstein J. Org. Chem.* **2013**, *9*, 2434–2445.

(14) (a) Subrizi, F.; Cardenas-Fernandez, M.; Lye, G. J.; Ward, J. M.; Dalby, P. A.; Sheppard, T. D.; Hales, H. C. *Green Chem.* **2016**, *18*, 3158–3165. (b) Leshch, Y.; Waschke, D.; Thimm, J.; Thiem, J. *Synthesis* **2011**, *2011*, 3871–3877. (c) Waschke, D.; Thimm, J.; Thiem, J. *Org. Lett.* **2011**, *13*, 3628–3631. (d) Osuch-Kwiatkowska, A.; Cieplak, M.; Jarosz, S. *Curr. Org. Chem.* **2014**, *18*, 327–340. (e) Jacobsen, A.; Thiem, J. *Curr. Org. Chem.* **2014**, *18*, 2833–2841.

(15) (a) Hale, K. J.; Hough, L.; Manaviar, S.; Calabrese, A. *Org. Lett.* **2015**, *17*, 1738–1741. (b) Hale, K. J.; Hough, L.; Manaviar, S.; Calabrese, A. *Org. Lett.* **2014**, *16*, 4838–4841.

(16) Garegg, P. J.; Regberg, T.; Stawiński, J.; Strömberg, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, 271–274.

(17) Zhong, Y.-L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622–2624.

(18) (a) Bichard, C. J. F.; Brandstetter, T. W.; Estevez, J. C.; Fleet, G. W. J.; Hughes, D. J.; Wheatley, J. R. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2151–2156. (b) Wheatley, J. R.; Beacham, A. R.; Lilley, P. M. de Q.; Watkin, D. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1994**, *5*, 2523–2534. (c) Bichard, C. J. F.; Wheatley, J. R.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1994**, *5*, 431–440.

(19) (a) Soengas, R.; Izumori, K.; Simone, M. I.; Watkin, D. J.; Skytte, U. P.; Soetaert, W.; Fleet, G. W. J. *Tetrahedron Lett.* **2005**, *46*, 5755–5759. (b) Hotchkiss, D. J.; Soengas, R.; Simone, M. I.; van Ameijde, J.; Hunter, S.; Cowley, A. R.; Fleet, G. W. J. *Tetrahedron Lett.* **2004**, *45*, 9461–9464.

(20) (a) Jenkinson, S. F.; Best, D.; Saville, A. W.; Mui, J.; Martinez, R. F.; Nakagawa, S.; Kunitatsu, T.; Alonzi, D. S.; Butters, T. D.; Norez, C.; Becq, F.; Blierot, Y.; Wilson, F. X.; Weymouth-Wilson, A. C.; Kato, A.; Fleet, G. W. J. *J. Org. Chem.* **2013**, *78*, 7380–7397. (b) Soengas, R. G.; Simone, M. I.; Hunter, S.; Nash, R. J.; Evinson, E. L.; Fleet, G. W. J. *Eur. J. Org. Chem.* **2012**, *2012*, 2394–2402. (c) Simone, M. I.; Edwards, A. A.; Tranter, G. E.; Fleet, G. W. J. *Amino Acids* **2011**, *41*, 643–661. (d) Best, D.; Jenkinson, S. F.; Saville, A. W.; Alonzi, D. S.; Wormald, M. R.; Butters, T. D.; Norez, C.; Becq, F.; Blierot, Y.; Adachi, I.; Kato, A.; Fleet, G. W. J. *Tetrahedron Lett.* **2010**, *51*, 4170–4174. (e) Glawar, A. F. G.; Jenkinson, S. F.; Newberry, S. J.; Thompson, A. L.; Nakagawa, S.; Yoshihara, A.; Akimitsu, K.; Izumori, K.; Butters, T. D.; Kato, A.; Fleet, G. W. J. *Org. Biomol. Chem.* **2013**, *11*, 6886–6899. (f) Lenagh-Snow, G. M. J.; Jenkinson, S. F.; Newberry, S. J.; Kato, A.; Nakagawa, S.; Adachi, I.; Wormald, M. R.; Yoshihara, A.; Morimoto, K.; Akimitsu, K.; Izumori, K.; Fleet, G. W. J. *Org. Lett.* **2012**, *14*, 2050–2053.

(21) Liu, Z.; Yoshihara, A.; Wormald, M. R.; Jenkinson, S. F.; Gibson, V.; Izumori, K.; Fleet, G. W. J. *Org. Lett.* **2014**, *16*, 5663–5665.

(22) (a) Frihed, T. G.; Bols, M.; Pedersen, C. M. *Chem. Rev.* **2015**, *115*, 3615–3676. (b) Bielski, R.; Witczak, Z. *J. Curr. Org. Chem.* **2014**, *18*, 1897–1912.

(23) (a) Sanapala, S. R.; Kulkarni, S. S. *Org. Lett.* **2016**, DOI: [10.1021/acs.orglett.6b01796](https://doi.org/10.1021/acs.orglett.6b01796). (b) Sanapala, S. R.; Kulkarni, S. S. *J. Am. Chem. Soc.* **2016**, *138*, 4938–4947.

(24) (a) Yoshihara, A.; Haraguchi, S.; Gullapalli, P.; Rao, D.; Morimoto, K.; Takata, G.; Jones, N. A.; Jenkinson, S. F.; Wormald, M. R.; Dwek, R. A.; Fleet, G. W. J.; Izumori, K. *Tetrahedron: Asymmetry* **2008**, *19*, 739–745. (b) Jones, N. A.; Jenkinson, S. F.; Soengas, R.; Fanefjord, M.; Wormald, M. R.; Dwek, R. A.; Kiran, G. P.; Devendar, R.; Takata, G.; Morimoto, K.; Izumori, K.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2007**, *18*, 774–786. (c) Gullapalli, P.; Yoshihara, A.; Morimoto, K.; Rao, D.; Jenkinson, S. F.; Fleet, G. W. J.; Izumori, K.; Akimitsu, K. *Tetrahedron Lett.* **2010**, *51*, 895–898.