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Room Temperature Regioselective Debenzylative Cycloetherification Reaction

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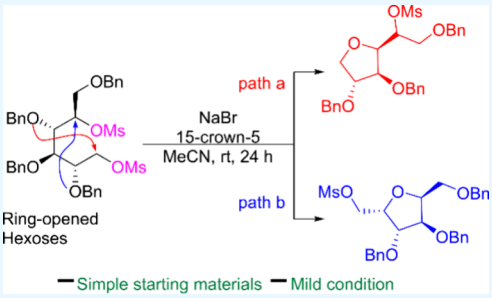
ABSTRACT: A regio- and stereoselective debenzylative cycloetherification (DBCE) reaction of protected hexoses to form stereodefined hydroxylated tetrahydrofurans of synthetic utility has been investigated under very mild room temperature reaction conditions. This study revealed the potential application of the DBCE reaction of simple, abundant starting materials to access stereochemically rich tetrahydrofuran compounds under mild reaction conditions.



INTRODUCTION

Hydroxylated tetrahydrofurans (THFs) are an important and unique structural moiety found in many natural products and other biologically active molecules.[1−7] For example, annonaceous acetogenins containing hydroxylated THFs such as mucoxin, obtusallene III, and the polyether X14766A have shown exceptional antitumor and antibacterial activity (Figure 1).[8−11] Quite recently, hydroxylated THF moieties have been explored to target GLUT5-transporters as a nonradiolabeled positron emission tomography (PET) imaging probe for potential applications in cancer therapy (Figure 1).[12]

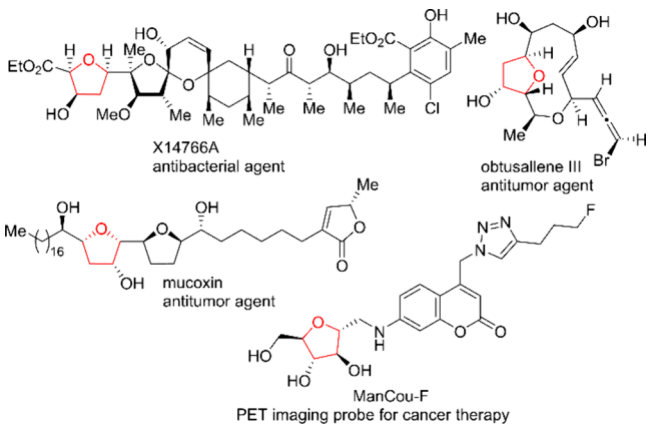


Figure 1. Pharmaceuticals containing hydroxylated tetrahydrofuran derivatives.

Despite their utility, the stereocontrolled synthesis of hydroxylated THF derivatives remains synthetically challenging due to their stereochemical complexity.[13] Synthetic methods targeting their preparation still remain the subject of active research.[14] The oxidation of alkenes, dienes, and polyenes remains an excellent approach to construct the motif in a stereoselective fashion. In 2003, Donohoe and co-workers reported the oxidative cyclization of 1,5-dienes for the construction of hydroxylated THF compounds (Scheme 1a).[15] Springboarding from earlier efforts to access the motif,[16−18] Borhan and co-workers developed a tactic that engaged chiral epoxy-alcohols (arising from Sharpless asymmetric epoxidation (SAE)) with dimethylsulfoxonium methylide to induce a nucleophilic ring-opening, Payne rearrangement, cyclization cascade that delivered 2,3-disubstituted hydroxylated THFs (Scheme 1b).[19] The same group also exploited the ionization and cyclization of orthoesters arising from chiral 1,2,n-triols to generate the motif (Scheme 1c).[20] These enabling technologies were subsequently leveraged to complete several enantioselective total syntheses of hydroxy-THF containing natural products.[21,22] Castillón and co-workers also constructed stereoselective hydroxylated THF by alkene haloetherification. This approach involves the electrophilic cycloetherification of 4-penten-1,2,3-triol to access the hydroxylated THF derivative (Scheme 1d).[23] Furthermore, other methods for accessing the motif include the intramolecular capture of reactive oxonium ion intermediates by tethered nucleophilic alkenes.[24,25] Additionally, cycloaddition and annulation reactions involving two- and three-atom components such as carbonyl ylides, cyclo-

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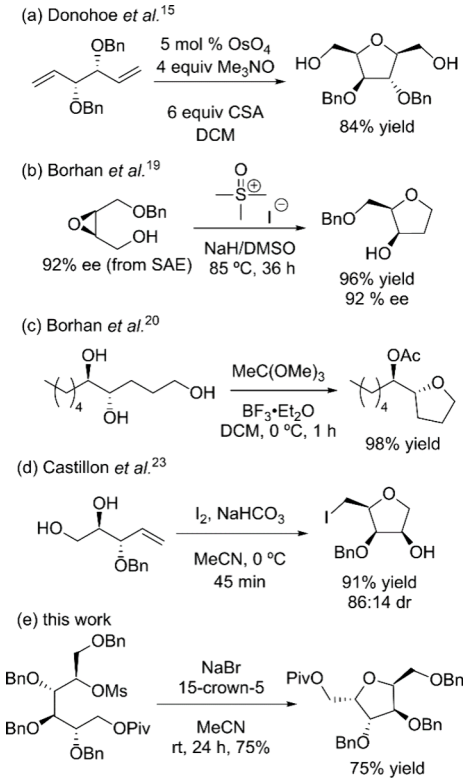
Scheme 1. Literature Reports and Our Approach



propanes, epoxides, and alkenes as well as O−H insertion into diazo-derived iron carbenes have also proven valuable in generating hydroxylated THFs.[26−28]

Despite these advances, some challenges remain including the need to access cumbersome starting materials through several synthetic steps, the use of metal catalysts, and the frequent isolation of diastereomeric mixtures. In the recent past, the debenzylative cycloetherification (DBCE) of linear carbohydrates has been explored to access stereospecific substituted THF derivatives.[29−36] The DBCE reaction normally involves a nucleophilic attack by the oxygen atom of a benzyl ether onto a carbon in the δ-position that bears an activated alcohol as a leaving group to give stereospecific tetrahydrofurans. It is noteworthy that this transformation traditionally requires rather high reaction temperatures (110−120 °C) and long reaction times.

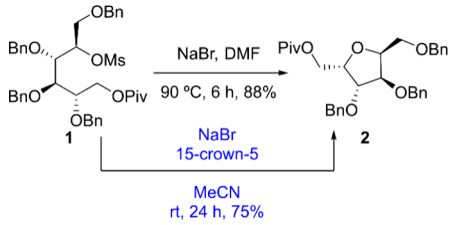
Herein, we report the development of regio- and stereoselective DBCE of acyclic carbohydrates to give hydroxylatyed THF derivatives under very mild reaction, room temperature conditions (Scheme 1e).

RESULTS AND DISCUSSION

To explore the DBCE transformation, the mesylate **1** was first subjected to reaction with sodium bromide in DMF at 90 °C over 6 h to afford cyclized product **2** in 88% yield (Scheme 2). Benzyl bromide was isolated as a stoichiometric byproduct. We then attempted to determine the feasibility of the DBCE reaction at ambient conditions. Intriguingly, treating **1** with sodium bromide and 15-crown-5 ether in CH_3CN at room temperature for 24 h gave a satisfactory yield of 75% of the desired cyclized product **2** as well.

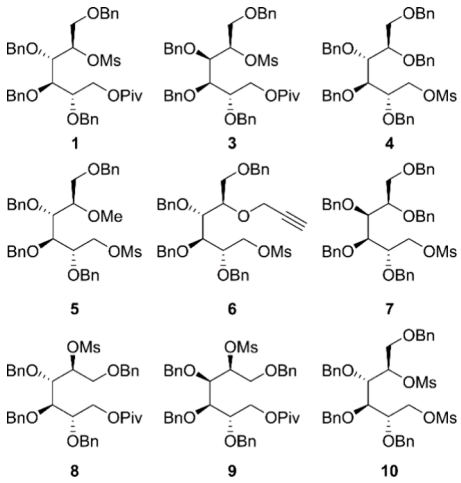
Moving forward, we explored the DBCE transformation under ambient conditions on the mesylates of tetra-O-

Scheme 2. Exploring the DBCE Reaction at Elevated and Room Temperatures to Access Hydroxylated THF



benzylated derivatives of D-glucose and D-galactose (Chart 1). The glucose derivatives **1** and **4** were investigated to show

Chart 1. Substrates Evaluated for DBCE Transformation



the stereospecific cyclization of the DBCE reaction through a nucleophilic attack on the primary and secondary sp^3 reactive centers. A similar transformation was also investigated with galactose derivatives **3** and **7**. The influence of the relative stereoconfiguration of the leaving group (activated alcohol) and the nucleophile on the DBCE transformation was also investigated with substrates **8** and **9** which are C5 epimers of substrates **1** and **3** respectively. Substrates **5** and **6** were also included to show the synthetic utility of this DBCE transformation. In addition, we investigated the regioselectivity of this DBCE transformation with dimesylate glucose derivative **10**. The synthesis of substrates **1** and **3**−**10** is outlined in detail in the ESI.

We next focused on the DBCE transformation of substrates **3**−**10** under ambient conditions. Recall that the reaction of mesylate-glucose derivative **1** with sodium bromide and 15-crown-5 ether in CH_3CN at room temperature for 24 h afforded the desired cyclized product **2** in 75% yield. To confirm the absolute stereochemistry of **2**, we envisioned that its di-O-*iso*-propylidene derivative **12** might yield a crystalline solid suitable for X-ray analysis. Thus, removal of the benzyl protecting groups of **2**, followed by subsequent treatment of the corresponding unprotected THF derivative **11** with $CuSO_4$ in acetone and a catalytic amount of H_2SO_4, afforded the di-O-*iso*-propylidene-THF derivative **12** in 95% yield. Gratifyingly, bis-ketal **12** formed a single crystal on slow evaporation of a 1:1 DCM/hexane solution of the compound (Scheme 3; SI Figures S1, S2, Table S1).

Following the DBCE reaction conditions above, the mesylate-galactose derivative **3** also conformed well to the

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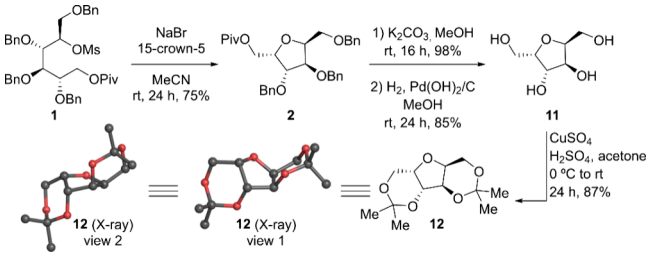
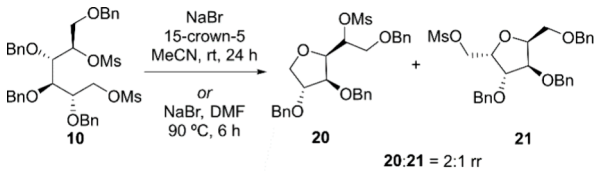
Scheme 3. DCBE of Mesylate 1 and Conversion to 12 for X-ray Analysis



DBCE reaction to give the desired cyclized product **13** in 66% yield (Scheme 4, eq 1). Primary mesylate substrates **4**−**7** were successfully converted to their respective THF derivatives **14**−**17** in satisfactory yields (**4** to **14**: 85%; **5** to **15**: 73%; **6** to **16**: 71%; **7** to **17**: 65%). Also, the C5 glucose and galactose epimers **8** and **9** provided THF products **18** and **19** in 64% and 62% yields, respectively. This shows that the relative stereoconfiguration of the leaving group (activated alcohol) and the nucleophile do not affect the DBCE transformation as long as the leaving group is located on a carbon which is four bonds away from the nucleophilic oxygen of the benzyl ether group.

Moving forward, we decided to investigate the regioselectivity of the DBCE reaction with dimesylate glucose derivative **10**. Interestingly, the reaction of **10** afforded both cyclized THF derivatives **20** and **21** in a 2:1 regioisomeric ratio (rr) determined from crude ^{1}H NMR (Scheme 5). To explore whether the reaction temperature could influence a regioselective DBCE cyclization favoring the formation of either **20** or **21**, we subjected compound **10** to reaction with sodium bromide in DMF at temperatures of 25, 50, 110, and 120 °C. At 25 °C for 24 h, the starting material was unchanged, with no detection of **20** or **21**. Increasing the temperature to 50 °C for 24 h resulted in more than 60% of the starting material remaining, with both **20** and **21** observed in the same 2:1 regioisomeric ratio. There was no significant difference observed at 110 °C for 6 h compared to the reaction at 90 °C. However, at 120 °C, neither the starting material nor products **20** or **21** were detected; ^{1}H NMR analysis indicated that the starting material decomposed at this temperature. Interestingly, when the reaction was conducted in acetonitrile

Scheme 5. DBCE of Bismesylate 10



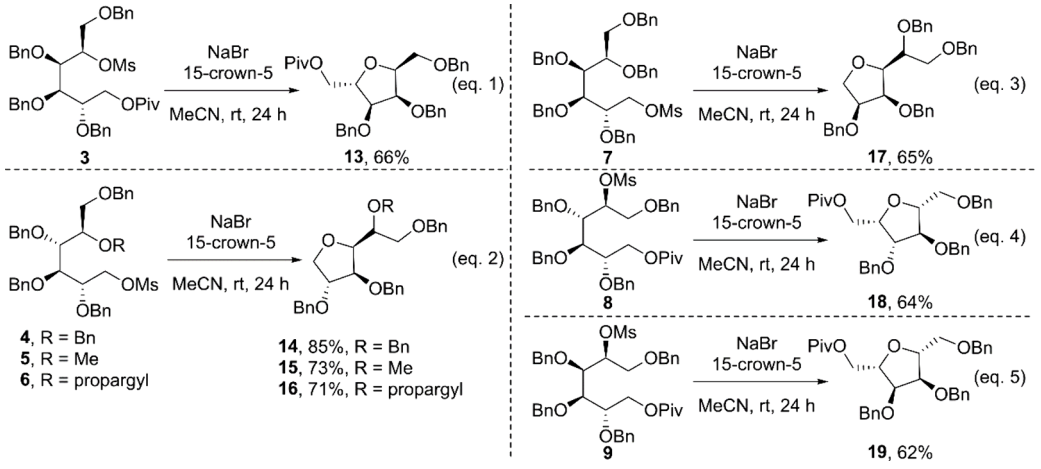
in the presence of 15-crown-5 at 90 °C, the reaction was completed in less than 1 h, with both **20** and **21** observed in the same 2:1 regioisomeric ratio. However, conducting the reaction at 0 °C in the presence of 15-crown-5 in either DMF or acetonitrile resulted in no conversion of the starting material. These results shed light on the mechanistic pathway of the reaction, indicating that ambient temperature is optimal for DBCE cyclization as long as sodium bromide is dissolved, which can be achieved by incorporating a phase transfer catalyst or increasing the reaction temperature. Furthermore, this suggests that the reaction progresses more favorably when the leaving group is positioned on a primary carbon atom rather than a secondary position, which is consistent with typical S_N2 processes.

The proposed mechanism of the DBCE reaction involves, first, an attack of the nucleophilic oxygen of the benzyl ether group onto the reactive sp^3-carbon bearing the activated alcohol in a classical S_N2 fashion to give either oxonium intermediate **Im-2** or **Im-5**. Subsequent attack by the bromide anion at the most electrophilic benzylic carbon gives the final cyclized products (Scheme 6).

CONCLUSIONS

In conclusion, we have investigated the debenzylative cycloetherification (DBCE) reaction of hexoses to form stereochemically defined hydroxylated THF derivatives of synthetic utility using a very mild, room temperature tansformation deploying sodium bromide and 15-crown-5 in acetonitrile. This work demonstrates the efficiency of the DBCE transformation under very mild reaction conditions, making it suitable for synthesizing a wide range of hydroxylated THF derivatives, including those with labile substituents that are of biological relevance.

Scheme 4. Expanded Substrate Scope of DBCE Reaction of Sugar Mesylates



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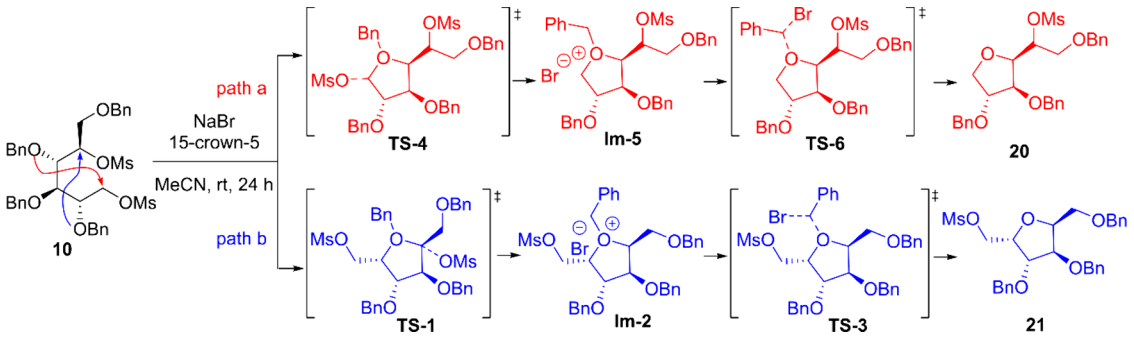
Scheme 6. Proposed Mechanism for DCBE Reaction of Bismesylate 10



EXPERIMENTAL SECTION

General Information. All reagents were purchased from commercial sources and used without purification, unless otherwise noted. Unless otherwise noted, all nonaqueous reactions were performed under an inert atmosphere of nitrogen in flame-dried glassware containing a stir bar. Acetonitrile (ACN), tetrahydrofuran (THF), dichloromethane (DCM), methanol (MeOH), dimethylformamide (DMF), and pyridine (py) were obtained from commercial sources and dried following standard distillation procedures. All other solvents were obtained from commercial sources and used without drying, unless otherwise noted. All water and aqueous solutions were made by using deionized (DI) water. Flash column chromatography was carried out using ZEOCHEM silica gel (40−63 μm). Analytical and preparative thin-layer chromatographies (TLC) were performed on Sorbtech silica G TLC plates. ^{1}H and ^{13}C NMR spectra were obtained using Bruker avance 500 MHz spectrometers. Chemical shifts are reported in parts per million (ppm). Spectra are referenced to residual solvent peaks. Infrared spectroscopy data were collected using an IR Affinity-1S instrument (with an MIRacle 10 single reflection ATR accessory). All known compounds were characterized by ^{1}H and ^{13}C NMR and are in complete agreement with samples reported elsewhere. All new compounds were characterized by ^{1}H and ^{13}CNMR, ATR-FTIR, HRMS, XRD, and melting points (where appropriate). HRMS data were collected using an instrument equipped with electrospray ionization in positive mode (ESI+) and a time-of-flight (TOF) detector.

Procedure for the Synthesis of Hydroxylated THFs. The following procedure was used for thermal cyclization. To a flame-dried round-bottom flask equipped with a water-cooled condenser and a stir bar were added NaBr (2 mmol, 2 equiv) and 5 mL of anhydrous DMF. To this stirring solution was added the mesylate hexose derivative (1 mmol, 1 equiv) in 2 mL of anhydrous DMF. The reaction mixture was then stirred at 90 °C for 6 h. Upon completion, water was added and the mixture was then extracted with ethyl acetate (3 × 25 mL), and the combined organic layer was dried over $MgSO_4$, filtered, and concentrated in a vacuum. The residue was purified by flash chromatography on silica gel with DCM and MeOH (100% DCM to 97:3 DCM/MeOH) to afford the corresponding hydroxylated THF derivatives.

The following procedure was used for the cyclization under ambient conditions. To a solution of NaBr (2 mmol, 2 equiv) and 15-crown-5 (3 mmol, 1.5 equiv) in 6 mL of anhydrous acetonitrile under nitrogen was added dropwise a solution of the mesylate hexose derivative (1 mmol, 1 equiv) in 4 mL of anhydrous acetonitrile. The reaction mixture was allowed to stir at room temperature for 24 h. Upon completion, water was added; the mixture was then extracted with ethyl acetate (3 × 25 mL), and the combined organic layer was dried over $MgSO_4$, filtered, and concentrated in a vacuum. The residue was purified by flash chromatography on silica gel with hexane and ethyl acetate (100% hexane to 90:10 hexane/ethyl acetate) to afford the corresponding hydroxylated THF derivative.

2 *(((2S,3R,4R,5S)-3,4-Bis(benzyloxy)-5-((benzyloxy)-methyl)tetrahydrofuran-2-yl)methyl pivalate).* Pale yellow oil; yield 75% (0.52 g), IR: 2941 (w), 2352 (w), 1731 (s), 1442 (m), 1283 (m), 1156 (m), 1078 (s), 1028 (m), 915 (m), 742 (w), 697 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.28 (m, 15H), 4.67 (d, J = 12.1 Hz, 1H), 4.61−4.57 (m, 3H), 4.56 (d, J = 3.2 Hz, 1H), 4.48 (d, J = 12.0 Hz, 1H), 4.46−4.43 (m, 1H), 4.41−4.37 (m, 1H), 4.36−4.33 (m, 1H), 4.10 (dd, J = 3.9, 1.5 Hz, 1H), 4.05 (dd, J = 4.0, 1.7 Hz, 1H), 3.82−3.73 (m, 2H), 1.25 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.33, 138.27, 137.85, 137.64, 128.55, 128.54, 128.41, 128.41, 127.97, 127.87, 127.74, 127.66, 127.64, 81.63, 81.20, 79.21, 77.96, 73.50, 72.45, 72.27, 68.31, 62.95, 38.76, 27.27; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{32}H_{39}O_6$ 519.2747; Found 519.2734.

13 *(((2S,3S,4R,5S)-3,4-Bis(benzyloxy)-5-((benzyloxy)-methyl)tetrahydrofuran-2-yl)methyl pivalate).* Pale yellow oil; yield 66% (0.46 g), IR: 2970 (w), 1724 (m), 1454 (m), 1358 (m), 1281 (m), 1153 (m), 1092 (m), 1061 (m), 1026 (s), 914 (m), 733 (w), 698 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.31 (m, 15H), 4.77 (d, J = 11.7 Hz, 2H), 4.73−4.69 (m, 1H), 4.65−4.62 (m, 2H), 4.61−4.56 (m, 3H), 4.52−4.49 (m, 1H), 4.40 (ddd, J = 10.3, 4.3, 2.0 Hz, 2H), 4.30−4.24 (m, 2H), 4.13 (q, J = 4.3 Hz, 1H), 4.10−4.06 (m, 1H), 3.64 (dd, J = 10.8, 3.4 Hz, 1H), 3.54 (dd, J = 10.7, 3.8 Hz, 1H), 1.23 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.36, 138.17, 138.08, 137.86, 128.42, 128.39, 128.36, 127.81, 127.79, 127.68, 127.66, 80.11, 79.22, 77.99, 77.59, 73.44, 73.35, 72.62, 69.92, 63.34, 38.77, 27.24; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{32}H_{39}O_6$ 519.2747; Found 519.2741.

14 *((2S,3S,4R)-3,4-Bis(benzyloxy)-2-((R)-1,2-bis-(benzyloxy)ethyl)tetrahydrofuran).* Pale yellow oil; yield 85% (0.60 g), IR: 2924 (w), 1454 (m), 1096 (s), 1057 (s), 1026 (m), 733 (m), 694 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44−7.28 (m, 20H), 4.88 (d, J = 11.5 Hz, 1H), 4.65 (d, J = 7.7 Hz, 2H), 4.59−4.55 (m, 3H), 4.53 (d, J = 12.4 Hz, 2H), 4.22−4.20 (m, 2H), 4.19−4.17 (m, 1H), 4.11 (d, J = 1.6 Hz, 1H), 4.11−4.08 (m, 1H), 3.97 (dd, J = 10.7, 2.0 Hz, 1H), 3.89 (dd, J = 9.9, 1.7 Hz, 1H), 3.77 (dd, J = 10.6, 5.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.02, 138.68, 137.97, 137.81, 128.50, 128.44, 128.32, 128.28, 127.83, 127.79, 127.67,

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127.65, 127.61, 127.44, 127.39, 81.66, 81.60, 79.78, 76.21, 73.47, 72.54, 72.08, 71.49, 71.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{34}H_{37}O_5$ 525.2641; Found 525.2637.

15 *((2S,3S,4R)-3,4-Bis(benzyloxy)-2-((R)-2-(benzyloxy)-1-methoxyethyl)tetrahydrofuran).* Pale yellow oil; yield 73% (0.46 g), IR: 2924 (m), 1454 (m), 1096 (s), 1057 (s), 1026 (m), 733 (w), 694 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.31 (m, 15H), 4.65−4.61 (m, 5H), 4.56−4.52 (m, 2H), 4.47 (d, J = 11.9 Hz, 1H), 4.19−4.16 (m, 1H), 4.16−4.14 (m, 1H), 4.11 (d, J = 3.5 Hz, 1H), 4.10−4.07 (m, 2H), 3.92 (dd, J = 10.7, 2.0 Hz, 1H), 3.85 (dd, J = 9.8, 1.8 Hz, 1H), 3.77 (ddd, J = 9.1, 5.1, 2.1 Hz, 1H), 3.69−3.62 (m, 2H), 3.47 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.64, 138.01, 137.78, 128.52, 128.48, 128.44, 128.29, 127.83, 127.81, 127.61, 127.41, 81.82, 81.45, 79.46, 77.42, 73.46, 72.19, 72.06, 71.31, 70.12, 57.91; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{33}O_5$ 449.2328; Found 449.2324.

16 *((2S,3S,4R)-3,4-Bis(benzyloxy)-2-((R)-2-(benzyloxy)-1-(prop-2-yn-1-yloxy)ethyl)tetrahydrofuran).* Pale yellow oil; yield 71% (0.43 g), IR: 2862 (m), 1454 (m), 1092 (s), 1057 (s), 1026 (m), 733 (m), 694 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40−7.30 (m, 15H), 4.69 (dd, J = 29.8, 18.1 Hz, 2H), 4.63−4.56 (m, 2H), 4.53 (d, J = 11.9 Hz, 1H), 4.49−4.45 (m, 1H), 4.45−4.42 (m, 1H), 4.26 (dd, J = 15.4, 2.5 Hz, 1H), 4.20−4.18 (m, 1H), 4.16 (dd, J = 9.9, 4.7 Hz, 1H), 4.11 (dd, J = 9.1, 3.4 Hz, 1H), 4.07 (dd, J = 2.7, 1.5 Hz, 1H), 4.06−4.03 (m, 1H), 3.94 (dd, J = 10.8, 1.9 Hz, 1H), 3.85 (dd, J = 9.9, 1.6 Hz, 1H), 3.71 (dd, J = 10.8, 5.8 Hz, 1H), 2.39 (t, J = 2.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.47, 137.99, 137.72, 128.48, 128.44, 128.33, 127.89, 127.84, 127.81, 127.61, 127.60, 127.48, 81.68, 81.27, 80.37, 79.46, 75.65, 74.11, 73.46, 72.40, 72.15, 71.28, 71.19, 57.83; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{33}O_5$ 473.2328; Found 473.2322.

18 *(((2S,3R,4R,5R)-3,4-Bis(benzyloxy)-5-((benzyloxy)-methyl)tetrahydrofuran-2-yl)methyl pivalate).* Pale yellow oil; yield 64% (0.44 g), IR: 2916 (w), 1728 (m), 1454 (m), 1281 (m), 1157 (m), 1088 (ms), 1072 (s), 1026 (m), 737 (m), 694 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41−7.23 (m, 15H), 4.59 (dd, J = 15.8, 12.1 Hz, 2H), 4.54−4.49 (m, 2H), 4.43−4.41 (m, 1H), 4.40−4.38 (m, 1H), 4.30 (d, J = 6.4 Hz, 1H), 4.27−4.23 (m, 1H), 4.19−4.12 (m, 2H), 3.99 (d, J = 3.2 Hz, 2H), 3.65 (dd, J = 9.9, 5.8 Hz, 1H), 3.55 (dd, J = 9.9, 6.8 Hz, 1H), 1.21 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.29, 138.16, 137.69, 137.60, 128.48, 128.46, 128.35, 127.87, 127.83, 127.79, 127.73, 127.63, 127.58, 83.26, 82.86, 82.78, 78.98, 73.33, 71.62, 71.53, 70.41, 62.74, 38.72, 27.21; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{32}H_{39}O_6$ 519.2747; Found 519.2744.

19 *(((2S,3S,4R,5R)-3,4-Bis(benzyloxy)-5-((benzyloxy)-methyl)tetrahydrofuran-2-yl)methyl pivalate).* Pale yellow oil; yield 62% (0.43 g), IR: 2928 (w), 1724 (m), 1281 (m), 1153 (m), 1084 (s), 1026 (s), 733 (m), 698 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.31 (m, 15H), 4.76 (dd, J = 19.0, 11.8 Hz, 2H), 4.68−4.61 (m, 3H), 4.57 (d, J = 11.9 Hz, 1H), 4.51 (dd, J = 11.5, 4.1 Hz, 1H), 4.35 (dd, J = 11.5, 7.4 Hz, 1H), 4.31−4.24 (m, 2H), 4.21−4.16 (m, 2H), 3.88 (dd, J = 10.1, 5.4 Hz, 1H), 3.76 (dd, J = 10.1, 6.6 Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.46, 138.35, 138.22, 137.95, 128.46, 128.40, 128.37, 127.83, 127.75, 127.69, 127.59, 127.57, 127.42, 79.35, 78.59, 78.33, 76.75, 73.48, 73.43, 73.17, 69.86, 64.99, 38.77, 27.27; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{32}H_{39}O_6$ 519.2747; Found 519.2743.

20 *((R)-2-(Benzyloxy)-1-((2R,3S,4R)-3,4-bis(benzyloxy)-tetrahydrofuran-2-yl)ethylmethanesulfonate).* Pale yellow oil; yield 65% (0.45 g), IR: 2866(w), 1454(m), 1173 (m), 1092 (m), 1076 (m), 737 (m), 694 (w), 602 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42−7.32 (m, 15H), 5.34−5.26 (m, 1H), 4.76 (d, J = 11.2 Hz, 1H), 4.64 (d, J = 11.8 Hz, 1H), 4.59−4.52 (m, 3H), 4.48 (d, J = 11.9 Hz, 1H), 4.24 (dd, J = 7.8, 3.5 Hz, 1H), 4.18 (dd, J = 3.5, 1.0 Hz, 1H), 4.13 (dd, J = 9.8, 4.4 Hz, 1H), 4.04 (dt, J = 4.4, 1.2 Hz, 1H), 3.97 (dd, J = 11.6, 2.1 Hz, 1H), 3.90−3.79 (m, 2H), 3.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.69, 137.66, 137.52, 128.55, 128.46, 128.27, 127.98, 127.96, 127.86, 127.84, 127.65, 81.19, 81.15, 79.20, 78.53, 73.33, 72.72, 72.39, 71.44, 70.35, 39.03; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{33}O_7S$ 513.1947; Found 513.1944.

21 *(((2S,3R,4R,5S)-3,4-Bis(benzyloxy)-5-((benzyloxy)-methyl)tetrahydrofuran-2-yl)methylmethanesulfonate).* Pale yellow oil; yield 30% (0.21 g), IR: 2913 (m), 1458 (m), 1288 (m), 1152 (m), 1085 (ms), 1078 (s), 1028 (m), 736 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−7.30 (m, 15H), 5.06−4.95 (m, 1H), 4.60−4.55 (m, 2H), 4.54−4.52 (m, 1H), 4.52−4.49 (m, 4H), 4.18−4.10 (m, 2H), 4.09−4.04 (m, 3H), 3.99−3.91 (m, 2H), 3.79−3.69 (m, 2H), 3.07 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.54, 137.46, 137.38, 128.54, 128.52, 128.50, 128.43, 127.94, 127.92, 127.89, 127.85, 127.83, 83.49, 82.93, 82.54, 80.72, 73.49, 72.06, 71.80, 71.29, 69.71, 38.62; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{33}O_7S$ 513.1947; Found 513.1944.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c04016.

Synthetic procedures for substrates **1**−**10**, X-ray data for **12**, and copies of ^1H and ^{13}C NMR spectra (PDF)

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Notes

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REFERENCES

(1) Bermejo, A.; Figadere, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. Acetogenins from Annonaceae: Recent Progress in Isolation, Synthesis and Mechanisms of Action. *Nat. Prod. Rep.* **2005**, *22* (2), 269−303.

(2) Saleem, M.; Kim, H. J.; Ali, M. S.; Lee, Y. S. An Update on Bioactive Plant Lignans. *Nat. Prod. Rep.* **2005**, *22* (6), 696−716.

(3) Faul, M. M.; Huff, B. E. Strategy and Methodology Development for the Total Synthesis of Polyether Ionophore Antibiotics. *Chem. Rev.* **2000**, *100* (6), 2407−2474.

(4) Kang, E. J.; Lee, E. Total Synthesis of Oxacyclic Macrodiolide Natural Products. *Chem. Rev.* **2005**, *105* (12), 4348−4378.

(5) Ritter, T. K.; Wong, C.-H. Carbohydrate-Based Drug Discovery in the Battle against Bacterial Infections: New Opportunities Arising from Programmable One-Pot Oligosaccharide Synthesis. In *Carbohydrate-Based Drug Discovery*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, FRG, 2005; pp 899−932.

(6) Wei, A. H.; Strickland, S. A., Jr; Hou, J.-Z.; Fiedler, W.; Lin, T. L.; Walter, R. B.; Enjeti, A.; Tiong, I. S.; Savona, M.; Lee, S.; Chyla, B.; Popovic, R.; Salem, A. H.; Agarwal, S.; Xu, T.; Fakouhi, K. M.; Humerickhouse, R.; Hong, W.-J.; Hayslip, J.; Roboz, G. J. Venetoclax Combined with Low-Dose Cytarabine for Previously Untreated Patients with Acute Myeloid Leukemia: Results from a Phase Ib/II Study. *J. Clin. Oncol.* **2019**, *37* (15), 1277−1284.

(7) Suzuki, M.; Okuda, T.; Shiraki, K. Synergistic Antiviral Activity of Acyclovir and Vidarabine against Herpes Simplex Virus Types 1 and 2 and Varicella-Zoster Virus. *Antiviral Res.* **2006**, *72* (2), 157−161.

(8) Alali, F. Q.; Liu, X. X.; McLaughlin, J. L. Annonaceous Acetogenins: Recent Progress. *J. Nat. Prod.* **1999**, *62* (3), 504−540.

(9) Jiang, Z.; Chen, R. Y.; Chen, Y.; Yu, D. Q. Donnaienin, a New Acetogenin Bearing a Hydroxylated Tetrahydrofuran Ring. *J. Nat. Prod.* **1998**, *61* (1), 86−88.

(10) Teruya, T.; Suenaga, K.; Maruyama, S.; Kurotaki, M.; Kigoshi, H. Biselides A-E: Novel Polyketides from the Okinawan Ascidian Didemnidae Sp. *Tetrahedron* **2005**, *61* (27), 6561−6567.

(11) Hayakawa, I.; Kigoshi, H.; Okamura, M.; Suzuki, K.; Shimanuki, M.; Kimura, K.; Yamada, T.; Ohyoshi, T. Total Synthesis of Biselide A, A Cytotoxic Macrolide of Marine Origin. *Synthesis (Mass.)* **2017**, *49* (13), 2958−2970.

(12) Oronova, A.; Tanasova, M. Late-Stage Functionalization through Click Chemistry Provides GLUT5-Targeting Glycoconjugate as a Potential PET Imaging Probe. *Int. J. Mol. Sci.* **2023**, *24* (1), 173.

(13) Wolfe, J. P.; Hay, M. B. Recent Advances in the Stereoselective Synthesis of Tetrahydrofurans. *Tetrahedron* **2007**, *63* (3), 261−290.

(14) Narayan, R. S.; Borhan, B. Synthesis of the Proposed Structure of Mucoxin via Regio-and Stereoselective Tetrahydrofuran Ring-Forming Strategies. *Journal of Organic Chemistry* **2006**, *71* (4), 1416−1429.

(15) Donohoe, T. J.; Butterworth, S. A General Oxidative Cyclization of 1, 5-Dienes Using Catalytic Osmium Tetroxide. *Angew. Chem.* **2003**, *115* (8), 978−981.

(16) Narayan, R. S.; Sivakumar, M.; Bouhlel, E.; Borhan, B. Regiochemical Control in Intramolecular Cyclization of Methylene-Interrupted Epoxydiols. *Org. Lett.* **2001**, *3* (16), 2489−2492.

(17) Travis, B.; Borhan, B. Oxidative Cyclization of 1, 4-Dienes to Yield 2, 3, 5-Trisubstituted Tetrahydrofuran-Diols. *Tetrahedron Lett.* **2001**, *42* (44), 7741−7745.

(18) Sivakumar, M.; Borhan, B. Regiochemical Control in Intramolecular Cyclizations of 2, 3-Epoxysulfides Mediated by Solvent Effects. *Tetrahedron letters* **2003**, *44* (29), 5547−5551.

(19) Schomaker, J. M.; Pulgam, V. R.; Borhan, B. Synthesis of Diastereomerically and Enantiomerically Pure 2, 3-Disubstituted Tetrahydrofurans Using a Sulfoxonium Ylide. *J. Am. Chem. Soc.* **2004**, *126* (42), 13600−13601.

(20) Zheng, T.; Narayan, R. S.; Schomaker, J. M.; Borhan, B. One-Pot Regio-and Stereoselective Cyclization of 1, 2, n-Triols. *J. Am. Chem. Soc.* **2005**, *127* (19), 6946−6947.

(21) Narayan, R. S.; Borhan, B. Synthesis of the Proposed Structure of Mucoxin via Regio-and Stereoselective Tetrahydrofuran Ring-Forming Strategies. *Journal of Organic Chemistry* **2006**, *71* (4), 1416−1429.

(22) Schomaker, J. M.; Borhan, B. Total Synthesis of Haterumalides NA and NC via a Chromium-Mediated Macrocyclization. *J. Am. Chem. Soc.* **2008**, *130* (37), 12228−12229.

(23) Bravo, F.; Dıaz, Y.; Castillón, S. Stereoselective Synthesis of Both Enantiomers of 1, 4-Anhydro-Alditols, 1, 4-Anhydro-2-Amino-Alditols and d-and l-Isonucleosides from 2, 3-O-Isopropylidene-d-Glyceraldehyde Using Iodine-Induced Cyclization as the Key Step. *Tetrahedron: Asymmetry* **2001**, *12* (11), 1635−1643.

(24) Kadota, I.; Kawada, M.; Gevorgyan, V.; Yamamoto, Y. Intramolecular Reaction of (γ-Alkoxyallyl) Stannane with Aldehyde: Origin of the Stereoselectivities. *Journal of Organic Chemistry* **1997**, *62* (21), 7439−7446.

(25) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M.; Woerpel, K. A. Stereoselective C-Glycosylation Reactions of Ribose Derivatives: Electronic Effects of Five-Membered Ring Oxocarbenium Ions. *J. Am. Chem. Soc.* **2005**, *127* (31), 10879−10884.

(26) Huisgen, R.; De March, P. Three-Component Reactions of Diazomalonic Ester, Benzaldehyde, and Electrophilic Olefins. *J. Am. Chem. Soc.* **1982**, *104* (18), 4953−4954.

(27) Peng, Z.-H.; Woerpel, K. A. Synthesis of (±)-5-e Pi-Citreoviral and (±)-Citreoviral and the Kinetic Resolution of an Allylic Silane by a [3+ 2] Annulation. *Org. Lett.* **2002**, *4* (17), 2945−2948.

(28) Kafle, P.; Ghosh, B.; Hunter, A. C.; Mukherjee, R.; Nicholas, K. M.; Sharma, I. Iron-Carbene Initiated O-H Insertion/Aldol Cascade for the Stereoselective Synthesis of Functionalized Tetrahydrofurans. *ACS Catal.* **2024**, *14*, 1292−1299.

(29) Jarosz, S.; Gajewska, A.; Luboradzki, R. Synthesis of Higher Carbon Sugars. Unexpected Rearrangement of Higher Sugar Allylic Alcohols. *Tetrahedron Asymmetry* **2008**, *19* (11), 1385−1391.

(30) Potopnyk, M. A.; Cmoch, P.; Cieplak, M.; Gajewska, A.; Jarosz, S. The Synthesis of Higher Carbon Sugars: A Study on the Rearrangement of Higher Sugar Allylic Alcohols. *Tetrahedron Asymmetry* **2011**, *22* (7), 780−786.

(31) Dondoni, A.; Massi, A.; Nuzzi, A. A Serendipitous Discovery of a New C-Furanosyl Glycine Synthesis via Thiazole- Based Amino-homologation of Hexopyranoses. *Synlett* **2007**, *2007*, 0303−0307.

(32) Martin, O. R.; Yang, F.; Xie, F. Spontaneous Cyclization of Triflates Derived from δ-Benzyloxy Alcohols: Efficient and General Synthesis of C-Vinyl Furanosides. *Tetrahedron Lett.* **1995**, *36* (1), 47−50.

(33) Yang, B.-H.; Jiang, J.-Q.; Ma, K.; Wu, H.-M. Stereospecific Cyclization to Form C-Furanosides. *Tetrahedron Lett.* **1995**, *36* (16), 2831−2834.

(34) Persky, R.; Albeck, A. An Unexpected Rearrangement during Mitsunobu Epimerization Reaction of Sugar Derivatives. *J. Org. Chem.* **2000**, *65* (12), 3775−3780.

(35) Tikad, A.; Delbrouck, J. A.; Vincent, S. P. Debenzylative Cycloetherification: An Overlooked Strategy for Complex Tetrahydrofuran Synthesis. *Chem. - Eur. J.* **2016**, *22*, 9456−9476.

(36) Tikad, A.; Delbrouck, J. A.; Vincent, S. P. Debenzylative Cycloetherification: An Overlooked Key Strategy for Complex Tetrahydrofuran Synthesis. *Chem. Eur. J.* **2016**, *22* (28), 9456−9476.

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