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An oxepinone route to carbohydrate based oxepines

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ABSTRACT

Oxepines are ring expanded analogs of glycals that can be used to prepare septanose carbohydrates. A route to carbohydrate based oxepines that utilizes oxepinones as a key intermediate has been developed. The oxepinone intermediates were prepared via an amine catalyzed cycloisomerization of furanose hemi-ketals. 1,2-Reduction of the oxepinones followed by acetylation provided the novel ring expanded enol ether products. Moderate diastereoselectivity was observed for the reduction based on the starting oxepinone. 1,4-Addition onto the oxepinones was also demonstrated. Overall, the syntheses reported here will allow for ready access to novel ring expanded carbohydrate analogs.

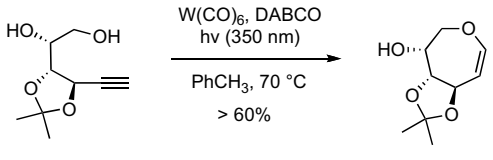
1. Introduction

The development of synthetic routes for the preparation of septanose carbohydrates continues to be an active area of research. Interest in this novel class of compounds owes primarily to the potential biological activities that they possess. A growing body of results suggest that septanosides and other polyhydroxylated seven-membered ring structures may be bound by proteins in a pyranose-mimetic fashion.[1,2] As in the synthesis of natural carbohydrates, attention has focused on the selective formation of glycosidic bonds involving the septanose residue. Glycosyl donor types include anomeric halides,[3] thioseptanosides,[4] and oxepines—cyclic enol ethers.[5,6]

Carbohydrate based oxepines have been key intermediates in our approach toward the synthesis of septanosides. Epoxidation of oxepines yields 1,2-anhydroseptanoses that are susceptible to nucleophilic attack.[5] Stereoselective epoxidation and inversion of the 1,2-anhydro species resulted in selective glycosidic bond formation.[7] Alternatively, trapping of the 1,2-anhydroseptanose with thiol/thiolate nucleophiles gave *S*-septanosides, which are donors in glycosylation reactions.[4] It was the versatility of oxepines that made them attractive synthetic targets.

Routes to carbohydrate based oxepines have employed ring closing metathesis (RCM),[8] cyclization–elimination,[9] and photocycloisomerization strategies.[6]

For example, McDonald has utilized a photocycloisomerization reaction to convert diols such as **1** to oxepines **2** (Eq. 1).[6] We wanted to know whether molecules akin to **4** (Eq. 2) could arise from diol **3** via the same reaction. The acetonide protecting group motif that was essential for cyclization of **1** was included in **3**. Reactant **3** differs, however, from **1** in two significant ways. First, the nucleophile in **1** is a primary alcohol whereas a secondary alcohol operates in **3**. Second, the nature of the propargylic groups of **1** and **3** is different. The propargylic group in **3** is a free alcohol but in **1** it is part of an acetonide. Between these two differences, the propargylic alcohol was expected to be especially problematic.



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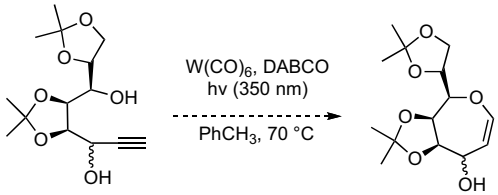

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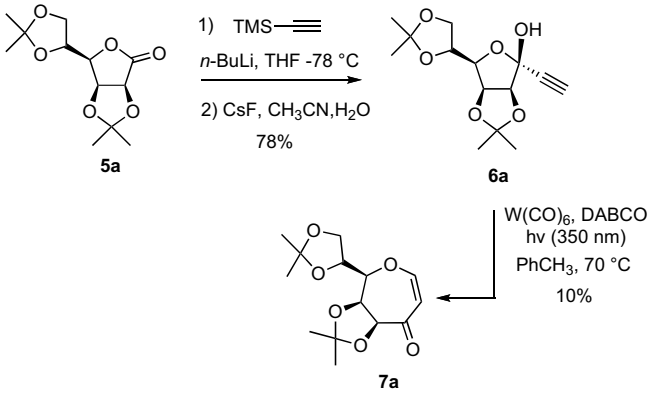
Diol **3**, prepared via acetylene addition to mannose di-acetonide, was subjected to the conditions of the McDonald photoisomerization. Repeated attempts resulted in recovery of the starting material. Other cycloisomerization conditions were also evaluated. Trost had demonstrated that a combination of Wilkinson's catalyst and phosphine ligands could be used to induce cycloisomerization of alkynols to generate cyclic enol ethers.[10] However, treatment of **3** under the Trost conditions failed to provide an oxepine product. We speculated that the propargylic alcohol present in **3** was interacting with the metal catalyst in such a manner as to prevent metal vinylidene formation.[11]

An alternative approach became evident during the investigation of the photocycloisomerization reaction. After attempts to selectively protect the propargylic alcohol as its benzyl or silyl ether failed, we proposed to convert it to the ketone. The ynone product (masked as the hemi-ketal) would facilitate a cyclization via conjugate addition to give an oxepinone that could be subsequently reduced to form the desired oxepine. Reported here is the synthesis of a small family of oxepines based on oxepinones as the key intermediates.

2. Results/discussion

As a corollary to the initial photoisomerization attempt, hemi-ketal **6a** was prepared as shown in Scheme 1. Under the conditions of the photocycloisomerization **6a** gave oxepinone **7a** in 10% yield. Despite the low yield, the result was encouraging because it suggested that the reaction could be optimized for the new starting materials. The reaction also indicated that the propargylic alcohol indeed affected the reaction as we had suspected.



Scheme 1.

A search for related reactions showed that **5b** (Fig. 1) had been converted to its corresponding oxepinone **7b** under related reaction conditions.[12] The reported process, however, was not a photocycloisomerization. Instead, simple addition of an amine base (triethylamine) to hemi-ketal **6b** affected cycloisomerization in high yield (95%). We reasoned that the DABCO used in the photocycloisomerization served the same role that TEA had in the reported oxepinone synthesis. When those reaction conditions (3 equiv TEA, DCM, rt) were employed, **6a** was again converted to **7a** in 10% yield. This confirmed the role of the trialkylamine and indicated that the reaction was proceeding via a pathway that did not require metals and/or photo-initiation. Nonetheless, the low yield in the cyclization reaction was puzzling. In an effort to understand the factors that contributed to the low yield, hemi-ketals **6b**–**6e** were prepared by TMS/acetylene addition to the corresponding lactones **5b**–**5e** followed by TMS deprotection.

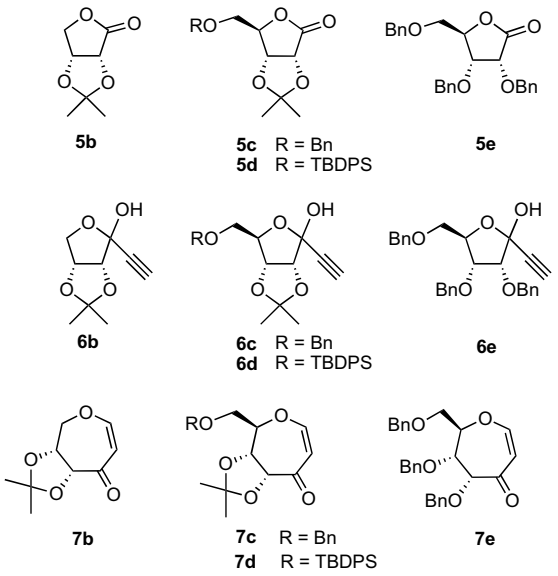


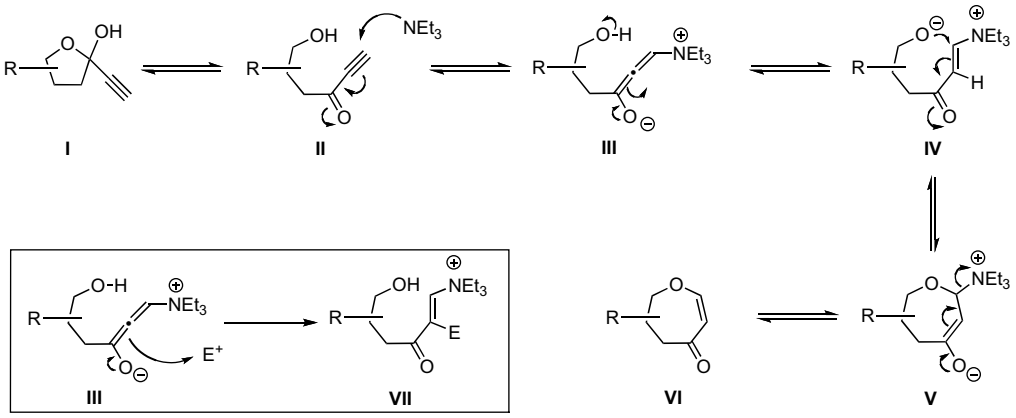
Figure 1.

Triethylamine mediated cyclization of **6a**–**6e** gave **7a**–**7e** in yields ranging from 8–41%. The highest yields in the group were for the D-ribonolactone derived hemi-ketals **6c** and **6d** (38% and 41%). In addition to the cyclization of **6a** to **7a** (10%), formation of the oxepinone derived from tri-*O*-benzyl D-ribonolactone (**7e**) was poor (8%). Notably, the yield for conversion of **6b** to **7b** was 31% in our hands. Higher yields correlate primarily with the presence of the rigidifying acetonide ring on the starting hemi-ketal (e.g., **6b**–**6d** vss **6e**). Hemi-ketal **6a** does not follow this trend, but its reduced cyclization efficiency may be due to multiple factors such as steric congestion around the nucleophilic oxygen or about the developing oxepinone itself.

Several parameters were varied in an effort to optimize the reaction. Variables included the identity of the amine (quinuclidine, DABCO, DBU, TEA),[13] equivalents of amine (cat., 1 equiv, 3 equiv), temperature (−78 °C, 0 °C, rt), and solvent (DCM, Et_2O, $CHCl_3$). Results from these experiments suggested that the reaction was unaffected when base or solvent was varied. The reaction was significantly slowed at −78 °C or when less than1 equiv of amine was used. We found that the initial conditions, adopted from the reported isomerization of **6b**, were the most efficient across all hemi-ketals investigated. We suggest that the lower yields for cyclization reported here better reflect the true efficiency of the reaction.

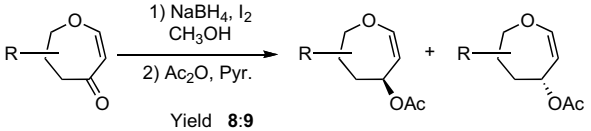
Consideration of the isomerization mechanism revealed intermediates where the reaction course could diverge from the cyclization pathway. The mechanism depicted in Scheme 2 shares features of Baylis–Hillman and oxa-Michael reactions. We propose that the reaction begins with the acyclic ynone species **II**, which is in equilibrium with hemi-ketal **I**. Triethylamine attack on **II** provides enone **IV** via **III**. Intramolecular attack by oxygen then gives cyclic species **V** that eliminates the β-triethylammonium group to form oxepinone **VI**. Direct intramolecular attack by oxygen onto ynone **II** is unlikely based on molecular orbital grounds.[14] In addition to potential side-reactions of the enone functionality in the product (**VI**), **III** may react with electrophiles other than H^+ such as **II**, **IV**, and **VI** (inset, Scheme 2). Taken together, these alternate pathways may partly explain the low yield of the desired oxepinones in this series.

Carbohydrate based oxepines are useful intermediates in the preparation of a number of septanose glycoconjugates; they were also the primary impetus for this synthetic investigation. In our



Scheme 2.

plan, oxepinones such as **7** were the penultimate intermediate in the preparation of oxepines. Conversion of the carbonyl group to an alcohol was necessary to complete the sequence. Reduction of oxepinones **7a**–**7d** utilized a procedure shown to be selective for 1,2-hydride attack.[16] In practice, reduction was followed by acetylation of the allylic alcohol to provide oxepines **8a**–**8d** and **9a**–**9d** as the C3 acetates. Yields (44–64%) and diastereomer ratios (10:1 to 1:3) for the two-step sequence are provided in Scheme 3. The configuration of diastereomers **8** and **9** was determined by H3,H4 ^3J coupling constant analysis. The facial selectivity observed for individual reductions is governed by the orientation of the dioxolane in the oxepinone starting material. In **7a**, for example, hydride attack opposite to the fused dioxolane should give rise to **8a** as the preferred product. A similar rationale explains **9b**–**9d** as the preferred products based on the α-dioxolane in **7b**–**7d**.

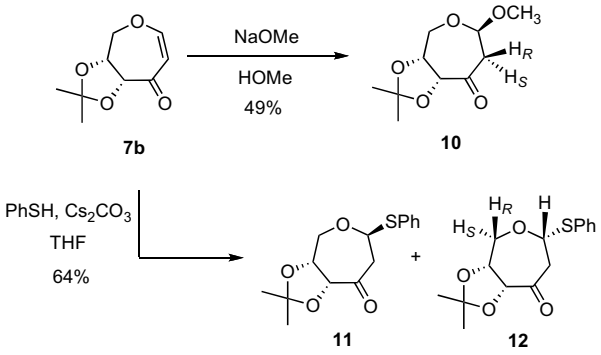


	Yield	8:9		
7a	64%	10:1	**8a**	**9a**
7b	44%	1:2	**8b**	**9b**
7c	62%	1:3	**8c** *	**9c**
7d	56%	1:3	**8d**	**9d**

Scheme 3. *Compound **8c** was isolated as the allylic alcohol. See note 15.

Yields of up to 18% for the five-step sequence (71% average yield per transformation) were obtained. While this synthesis of oxepines is less efficient than our RCM based approach, it is similar in efficiency to the cyclization–elimination approach we have described. It has the added advantages, however, of accommodating acid sensitive functionalities, which was not possible with the cyclization-elimination protocol, and scaleability, which is troublesome in the RCM approach.

The enone functionality in the oxepinones **7** provided an opportunity to access novel oxepanone structures. This reactivity was demonstrated using **7b** as a model (Scheme 4). Methoxide addition to **7b** gave **10** in 49% yield as a single diastereomer. Addition of thiophenol to **7b** provided a 1:1 mixture of the diastereomeric *S*,*O*-acetals **11** and **12** (64% combined yield). Stereochemistry at C1 in **10**–**12** was assigned based on NOESY spectra taken on **10** and **12**. Compound **10** was assigned based on an NOE between the methyl group of the methyl acetal and the *pro-R* H2. Oxepanone **12**, on the other hand, showed NOEs between H1 and the *pro-R* H6.[17] The highly substituted oxepanones **10**–**12** suggest potential routes to



Scheme 4.

2-deoxy septanoside structures. For example, 1,4-addition of carbohydrate based nucleophiles to **7b** would give more elaborate glycosides akin to **10**. Similarly, the mixed *S*,*O*-acetals **11** and **12** could be used as glycosyl donors in standard glycosylation reactions. These possibilities underscore the potential utility of the carbohydrate derived oxepinones in the synthesis of septanose carbohydrates.

3. Conclusion

Key contributions reported in this work range from the details of the synthesis of oxepinones to the intermediacy of oxepinones in the synthesis of oxepines and oxepanones. First, furanose hemiketals **6** were converted to oxepinones **7** in an amine base mediated isomerization. The results for several hemi-ketals collected here suggest that the efficiency of the reaction is lower than that reported earlier. We speculate that the lower yields are due to side-reactions that arise from the inherent reactivity of the product as well as via intermediates in the isomerization process. The oxepinone products were subsequently converted to the corresponding oxepines via 1,2-reduction. This route to carbohydrate based oxepines is complementary to others in the literature. We have also demonstrated the conversion of oxepinones to oxepanones via conjugate addition of methoxide and thiophenylate nucleophiles. Overall, the syntheses reported here will allow for ready access to novel ring expanded carbohydrate analogs.

4. Experimental

4.1. General

Unless stated otherwise, all reactions were conducted at room temperature (rt) under nitrogen atmosphere. Reactions were

monitored by TLC (silica gel, 60 Å, F_{254}, 250 μm). Visualization was conducted either under UV light or by charring with 2.5% *p*-anisaldehyde in H_2SO_4, acetic acid, and ethanol solution or aqueous $KMnO_4$, K_2CO_3, and KOH. Preparative chromatography was conducted on silica gel (60 Å, F_{254}, 250 μm). Melting points are uncorrected. Optical rotations were measured at 22±2 °C. ^{1}H NMR spectra were collected at either 400 MHz or 300 MHz with chemical shifts referenced to $CHCl_3$ (δ_H 7.27 ppm). ^{13}C NMR were collected at 100 MHz or 75 MHz and referenced to $CDCl_3$ (δ_C 77.2 ppm). Known compounds **5b**,[12] **5c**,[18] **5d**,[19] **6b**,[12] and **7b**[12] that were prepared by us gave physical data that were in accordance with the literature.

4.2. [4,5:7,8]-Di-*O*-isopropylidene-1,2-dideoxy-D-*manno*-hept-1-ynitol (3)

Ethylene diamine/lithium acetylide (2.12 g, 23.1 mmol) was dissolved in THF (50 mL). This solution was cooled to 0 °C, and HMPA (1.34 mL, 7.68 mmol) was added. In a separate flask, [2,3:5,6]-di-*O*-isopropylidene-D-mannose (2.00 g, 7.68 mmol) was dissolved in THF (20 mL). This solution was cooled to 0 °C and *n*-BuLi was added dropwise. After 0.5 h, the furanose solution was added dropwise to the lithium acetylide solution at 0 °C. The reaction mixture was allowed to warm to rt and was stirred overnight. After, excess base was quenched with the addition of a saturated solution of NH_4Cl (20 mL). The reaction mixture was concentrated in vacuo and the remaining aqueous layer was extracted with DCM (3×100 mL) and purified by column chromatography (7:3 Hex/EtOAc) to give **3** (1.34 g, 79%) as a white solid. ^{1}H NMR 300 MHz ($CDCl_3$) δ 4.78 (dd, *J*=2.1, 6.3 Hz, 1H), 4.48 (dd, *J*=7.3, 0.8 Hz, 1H), 4.35 (dd, *J*=6.8, 6.9 Hz, 1H), 4.08 (m, 3H), 3.86 (d, *J*=6.8 Hz, 1H), 2.55 (s, 1H), 1.55 (s, 3H), 1.42 (d, *J*=5.0 Hz, 6H), 1.36 (s, 3H); ^{13}C NMR 75 MHz ($CDCl_3$) δ 109.4, 109.1, 81.5, 79.7, 76.2, 75.3, 74.7, 69.6, 67.0, 61.3, 26.8, 26.5, 25.3, 24.6.

4.3. [2,3:5,6]-Di-*O*-isopropylidene-D-*manno*-lactone (5a)

To a solution of oxalyl chloride (2.33 mL, 27.05 mmol) in DCM (6 mL) cooled to −60 °C, a solution of DMSO (5.83 mL, 54.1 mmol) in DCM (6 ml) was slowly added and stirred for 5 min. A solution of [2,3:5,6]-di-*O*-isopropylidene-D-mannose (6.4 g, 24.6 mmol) in DCM (96 mL) was then added dropwise to the reaction mixture and stirred for 15 min. Triethyl amine (34.3 mL, 249.5 mmol) was then added dropwise to the reaction mixture and stirred for 10 min. The mixture was warmed to rt and stirred for an additional 1 h. The reaction was quenched with H_2O (30 mL) and extracted with DCM (3×30 mL). The combined organic layers were then washed with H_2O (3×30 mL), brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography using (4:1 Hex/EtOAc) as eluent to give the lactone as a white solid (4.5 g, 71%). Mp 121–124 °C; R_f 0.5 (7:3 Hex/EtOAc); $[\alpha]_D$ +55.6 (*c* 0.66, $CHCl_3$); ^{1}H NMR 300 MHz ($CDCl_3$) δ 4.86 (dd, *J*=5.2, 3.1 Hz, 1H), 4.83 (d, *J*=5.3 Hz, 1H), 4.4 (m, 2H), 4.13 (dd, *J*=9.2, 5.7 Hz, 1H), 4.05 (dd, *J*=9.2, 3.7 Hz, 1H), 1.46 (s, 3H), 1.45 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H); ^{13}C NMR 75 MHz ($CDCl_3$) δ 173.4, 114.5, 109.9, 78.2, 76.1, 75.9, 72.6, 66.5, 27.0, 26.8, 25.9, 25.1; HRMS *m*/*z* for $C_{12}H_{18}O_6Na$ calcd 281.1001, found 281.1017.

4.4. General procedure for formation of hemi-ketals from furanolactones

TMS/acetylene (1.8 mL, 12.65 mmol) in THF (15 mL) was cooled to −78 °C under N_2. To this was added a hexanes solution of *n*-BuLi (8.3 mL, 1.6 M) dropwise. The reaction mixture was stirred for 30 min at −78 °C and then a solution of **5** (6.32 mmol) in 10 mL THF was added. The reaction was maintained at −78 °C for 2 h and then quenched with satd NH_4Cl (aq) (25 mL). The aqueous phase was extracted with EtOAc (3×50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (3:1 Hex/EtOAc) to yield a mixture of the TMS-protected material and the deprotected product **6**. The TMS group of the protected material was then removed under conditions noted below to give **6a**–**6e**.

*4.4.1. 1-Ethynyl-[2,3:5,6]-di-O-isopropylidene-D-manno-furanose (**6a**).* To a solution of the TMS-protected analog of alkyne **6a** (1.26 g, 3.53 mmol) in MeCN/H_2O (45 mL:1.5 mL) at 0 °C was added CsF (0.644 g, 4.24 mmol) in two portions at an interval of 10 min. The reaction mixture was allowed to warm to rt and stirred for 4 h. The reaction was then quenched with H_2O (30 mL) and extracted with Et_2O (3×30 mL). The organic layer was washed with H_2O (3×20 mL) and brine (20 mL), then dried with Na_2SO_4 and concentrated in vacuo. The crude material was purified by column chromatography (3:1 Hex/EtOAc) to yield **6a** as a white solid (0.86 g, 86%). The combined yield of the two-step sequence was 78%. Mp 128–130 °C; $[\alpha]_D$ +47.8 (*c* 0.56, $CHCl_3$); ^{1}H NMR 400 MHz ($CDCl_3$) δ 4.86 (dd, *J*=5.6, 3.6 Hz, 1H), 4.61 (d, *J*=5.7 Hz, 1H), 4.44 (m, 1H), 4.14–4.02 (m, 3H), 3.60 (s, 1H), 2.73 (s, 1H), 1.53 (s, 3H), 1.46 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H); ^{13}C NMR 100 MHz ($CDCl_3$) δ 113.5, 109.4, 99.1, 86.6, 79.9, 79.4, 79.3, 74.7, 73.0, 72.6, 66.6, 26.9, 26.0, 25.2, 24.9; HRMS *m*/*z* for $C_{14}H_{20}O_6Na$ calcd 307.1158, found 307.1183.

*4.4.2. 1-Ethynyl-[2,3]-O-isopropylidene-5-O-benzyl-D-ribofuranose (**6c**).* CsF (0.24 g, 1.55 mmol) was added to a solution of TMS-protected analog of alkyne **6c** (0.54 g, 1.29 mmol) in MeCN/H_2O (30 mL:1 mL). The reaction mixture was stirred for 4 h at rt. After, H_2O and (50 mL) and EtOAc (200 mL) were added. The organic phase was separated, dried over Na_2SO_4, and concentrated in vacuo yielding **6c** (0.37 g, 95%) as an oil in a 3:1 mixture of diastereomers. The combined yield of the addition–deprotection sequence was 76%. R_f 0.5 (7:3 Hex/EtOAc); $[\alpha]_D$ −38.7 (*c* 0.47, $CHCl_3$); ^{1}H NMR 400 MHz ($CDCl_3$) δ 7.41–7.26 (m, 20H), 5.21 (s, 3H), 4.83 (dd, *J*=5.8, 1.2 Hz, 3H), 4.80 (m, 1H), 4.65, (s, 1H), 4.62 (s, 3H), 4.61–4.52 (m, 10H), 4.43 (m, 3H), 4.34 (m, 1H), 3.64 (dd, *J*=3.6, 3.6 Hz, 8H), 2.71 (s, 3H), 2.59 (s, 1H), 1.60 (s, 3H), 1.56 (s, 9H), 1.40 (s, 3H), 1.36 (s, 9H); ^{13}C NMR 100 MHz ($CDCl_3$) δ 136.1, 129.8, 128.8, 128.5, 128.4, 128.1, 127.8, 113.4, 101.5, 88.4, 85.2, 85.1, 82.1, 81.7, 81.4, 79.3, 74.1, 74.0, 73.5, 72.5, 70.8, 69.5, 26.6, 26.2, 25.4, 25.0; HRMS *m*/*z* for $C_{17}H_{20}O_5Na$ calcd 327.1208, found 327.1179.

*4.4.3. 1-Ethynyl-[2,3]-O-isopropylidene-5-O-t-butyldiphenylsilyl-D-ribofuranose (**6d**).* To a solution of the TMS-protected analog of alkyne **6d** (1.02 g, 1.94 mmol) in MeCN (20 mL) cooled to −20 °C was added K_2CO_3 (0.081 g, 0.58 mmol) in two portions at an interval of 10 min. The mixture was allowed to warm to 0 °C and then stirred for 2 h. The reaction was quenched with H_2O (30 mL) and extracted with Et_2O (3×30 mL). The organic layer was washed with H_2O (3×20 mL) and brine (20 mL), then dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by column chromatography (3:1 Hex/EtOAc) to yield a 3:1 diastereomeric mixture of **6d** as a yellow oil (0.249 g, 28%). The combined yield for the addition–deprotection sequence was 25%. ^{1}H NMR 300 MHz ($CDCl_3$) δ 7.77–7.67 (m, 16H), 7.48–7.39 (m, 24H), 4.90 (dd, *J*=6.8, 2.5 Hz, 1H), 4.85 (dd, *J*=5.8, 1.2 Hz, 3H), 4.79 (s, 3H), 4.76 (d, *J*=6.6 Hz, 1H), 4.63 (d, *J*=5.8 Hz, 3H), 4.38 (s, 1H), 4.36 (m, 3H), 4.30 (m, 1H), 3.86 (dd, *J*=4.9, 4.9 Hz, 3H), 3.83 (d, *J*=5.1 Hz, 2H), 3.71 (dd, *J*=11.2, 4.0 Hz, 1H), 2.67 (s, 3H), 2.49 (s, 1H), 1.60 (s, 3H), 1.56 (s, 9H), 1.40 (s, 3H), 1.38 (s, 9H), 1.13 (s, 27H); ^{13}C NMR 75 MHz ($CDCl_3$) δ 135.7, 135.6, 133.2, 133.0, 132.1, 132.0, 130.3, 130.1, 129.9, 129.8, 128.0 (2), 127.8 (2), 115.2, 113.3, 101.0, 96.1, 87.9, 86.8, 85.3, 82.7, 82.5, 82.0, 81.4, 79.5, 74.2, 72.5, 65.1, 63.3, 60.4, 31.6, 26.9, 26.7, 26.2,

25.6, 25.0, 22.6, 21.0, 19.2, 19.1, 14.2, 14.1; HRMS *m*/*z* for $C_{26}H_{32}O_5SiNa$ calcd 475.1917, found 475.1874.

*4.4.4. 1-Ethynyl-2,3,5-tri-O-benzyl-D-ribofuranose (**6e**).* To a solution of **3e** (0.76 g, 1.47 mmol) in MeCN/H_2O (45 mL:1.5 mL) cooled to 0 °C, CsF (0.268 g, 1.77 mmol) was added in two portions at an interval of 10 min. The reaction mixture was allowed to warm to rt and stirred for 4 h and then quenched with H_2O (30 mL). The product was extracted from the mixture with Et_2O (3×30 mL). The combined organic layers were washed with H_2O (3×20 mL) and brine (20 mL) then dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by column chromatography (3:1 Hex/EtOAc) to yield **4e** as a pale yellow oil (0.388 g, 60%). The combined yield for the addition–deprotection sequence was 37%. R_f 0.4 (7:3 Hex/EtOAc); ^{13}C NMR 75 MHz ($CDCl_3$) δ 186.5, 137.8, 137.7, 137.5, 137.3, 137.2, 137.1, 137.0, 128.2, 128.2, 128.2, 128.1, 128.0, 127.9, 127.8, 127.8, 127.8, 127.7, 127.6, 127.5, 127.4, 98.9, 95.7, 83.5, 82.1, 81.8, 81.5, 81.3, 80.6, 80.5, 80.4, 77.7, 77.4, 77.2, 73.6, 73.3, 73.1 (3), 72.7, 72.6, 72.3, 71.9, 70.3, 69.5, 69.3, 68.9; HRMS *m*/*z* for $C_{28}H_{28}O_5Na$ calcd 467.1834, found 467.1811.

4.5. General cycloisomerization procedure

To a rt solution of hemi-ketal **6** (3.00 mmol) in 150 mL $CHCl_3$ was added TEA (0.89 mL, 6.35 mmol). The mixture was stirred for 30 min and then concentrated in vacuo. The crude material was purified by column chromatography (3:1 Hex/EtOAc) to give the oxepinone product **7**.

*4.5.1. Z-(5R,6R-[2,2]-Dimethyl-1,3-dioxolo)-7R-(3S-[2,2]-dimethyl-1,3-dioxolanyl)-oxepin-4-one (**7a**).* Obtained as a pale yellow oil (10%). $[\alpha]_D$ +62.8 (*c* 1.14, $CHCl_3$); ^{1}H NMR 300 MHz ($CDCl_3$) δ 7.03 (d, *J*=6.6 Hz, 1H), 5.23 (dd, *J*=6.6, 1.7 Hz, 1H), 4.72 (d, *J*=7.4 Hz, 1H), 4.58 (dd, *J*=7.4, 1.7 Hz, 1H), 4.34 (ddd, *J*=6.2, 8.0, 4.5 Hz, 1H), 4.10 (dd, *J*=9.0, 6.2 Hz, 1H), 3.91 (dd, *J*=9.0, 4.5 Hz, 1H), 3.79 (d, *J*=8.0 Hz, 1H), 1.51 (s, 3H), 1.33 (m, 9H); ^{13}C NMR 75 MHz ($CDCl_3$) δ 197.3, 159.5, 111.9, 110.2, 106.9, 86.4, 84.0, 78.6, 73.7, 67.0, 27.0, 26.0, 25.5, 25.3; HRMS *m*/*z* for $C_{14}H_{21}O_6$ calcd 285.1338, found 285.1337.

*4.5.2. Z-(5S,6S-[2,2]-Dimethyl-1,3-dioxolo)-7R-benzyloxymethyl-oxepin-4-one (**7c**).* Obtained as a pale yellow oil in 38% yield. R_f 0.36 (7:3 Hex/EtOAc); $[\alpha]_D$ +47.9 (*c* 0.86, $CHCl_3$); ^{1}H NMR 400 MHz ($CDCl_3$) δ 7.40–7.30 (m, 5H), 7.15 (d, *J*=7.2 Hz, 1H), 5.29 (d, *J*=7.1 Hz, 1H), 4.81 (d, *J*=7.8 Hz, 1H), 4.72 (dd, *J*=10.2, 1.2 Hz, 1H), 4.65 (d, *J*=6.24 Hz, 2H), 4.10 (ddd, *J*=10.2, 5.1, 2.0 Hz, 1H), 3.86 (m, 2H), 1.57 (s, 2H), 1.52 (s, 3H), 1.43 (s, 3H); ^{13}C NMR 100 MHz ($CDCl_3$) δ 195.1, 159.2, 128.5, 127.8, 127.7, 110.5, 106.0, 83.8, 83.6, 76.2, 73.7, 69.5, 27.0, 25.2; HRMS *m*/*z* for $C_{17}H_{20}O_5Na$ calcd 327.1208, found 327.1185.

*4.5.3. Z-(5S,6S-[2,2]-Dimethyl-1,3-dioxolo)-7R-tert-butyldiphenylsil-oxymethyl-oxepin-4-one (**7d**).* Obtained as a clear colorless oil (41%). R_f 0.4 (7:3 Hex/EtOAc); $[\alpha]_D$ +70.5 (*c* 0.24, $CHCl_3$); ^{1}H NMR 300 MHz ($CDCl_3$) δ 7.67–7.80 (m, 4H), 7.52–7.32 (m, 6H), 7.12 (d, *J*=7.1 Hz, 1H), 5.28 (d, *J*=7.1 Hz, 1H), 4.79 (m, 2H), 4.05 (m, 3H), 1.49 (s, 3H), 1.40 (s, 3H), 1.11 (s, 9H); ^{13}C NMR 75 MHz ($CDCl_3$) δ 195.5, 159.6, 135.8(2), 133.4, 133.3, 130.0, 129.9, 127.9, 127.8, 110.6, 106.0, 85.4, 83.7, 76.2, 64.0, 27.0, 26.9, 25.3, 19.5; HRMS *m*/*z* for $C_{26}H_{32}O_5SiNa$ calcd 475.1917, found 475.1909.

*4.5.4. Z-(5S,6S-Di-O-benzyl)-7R-benzyloxymethyl-oxepin-4-one (**7e**).* Obtained as a clear colorless oil (8%). R_f 0.4 (8:2 Hex/EtOAc); $[\alpha]_D$ +77.2 (*c* 0.55, $CHCl_3$); ^{1}H NMR 300 MHz ($CDCl_3$) δ 7.45-7.24 (m, 15H), 7.22 (d, *J*=6.7 Hz, 1H), 5.54 (d, *J*=6.6 Hz, 1H), 4.96 (d, *J*=5.7 Hz, 1H), 4.93 (d, *J*=6.0 Hz, 1H), 4.60-4.42 (m,6H), 4.38 (dd, *J*=7.5, 3.4 Hz, 1H), 4.08 (ddd, *J*=11.5, 7.9, 4.0 Hz, 1H), 3.58 (m, 2H); ^{13}C NMR 75 MHz ($CDCl_3$) δ 195.1, 161.5, 137.9, 137.5, 128.5, 128.4, 128.3 (2), 127.9, 127.7, 127.6, 112.3, 85.7, 85.6, 80.3, 74.0, 73.4, 72.6, 69.5; HRMS *m*/*z* for $C_{28}H_{28}O_5Na$ calcd 467.1834, found 467.1835.

4.6. General procedure for 1,2-reduction and acetylation of oxepinones

To a solution of **7** (0.500 mmol) in THF (10 mL) cooled to 0 °C under N_2 was added $NaBH_4$ (0.022 g, 0.600 mmol). Next iodine (0.035 g, 0.136 mmol) in a solution of THF (10 mL) was added dropwise over 30 min. The reaction mixture was stirred at 0 °C for an additional 10 min and then quenched with 5 mL of a 1:1 H_2O/DCM mixture. Product material was then extracted with DCM (3×5 mL). The combined organic layers were washed with H_2O (3×5 mL) and brine (2×5 mL), then dried over Na_2SO_4 and concentrated in vacuo. The residue was then dissolved in DCM (20 mL) and cooled to 0 °C under N_2. DMAP (0.005 g, 0.04 mmol), Et_3N (0.064 mL, 0.461 mmol), and Ac_2O (0.064 mL, 0.678 mmol) were added sequentially and the reaction mixture was allowed to warm to rt overnight. The reaction was quenched by the addition 20 mL of NH_4Cl (aq) solution. Products were then extracted from the reaction mixture using DCM (3×5 mL). The organic layers were washed with H_2O (3×5 mL) and brine (2×5 mL), then dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by column chromatography (4:1 Hex/EtOAc) to yield product oxepines.

*4.6.1. 1,6-Anhydro-[4,5;7,8]-di-O-isopropylidene-3-O-acetyl-2-deoxy-D-glycero-D-talosept-1-enitol (**8a**).* Obtained as an off-white solid in 59% yield. R_f 0.4 (8:2 Hex/EtOAc); $[\alpha]_D$ +8.0 (*c* 1.26, $CHCl_3$); ^{1}H NMR 300 MHz ($CDCl_3$) δ 6.21 (dd, *J*=7.5, 2.3 Hz, 1H), 6.04 (m,1H), 4.55 (m,2H), 4.33 (ddd, *J*=7.3, 1.7, 1.7 Hz, 1H), 4.21 (ddd, *J*=8.2, 6.3, 4.7 Hz, 1H), 4.08 (dd, *J*=8.7, 6.3, Hz, 1H), 3.9 (dd, *J*=8.9, 4.6 Hz, 1H), 3.84 (d, *J*=8.2 Hz, 1H), 1.53 (s,3H), 1.41 (s, 3H), 1.40 (s, 3H), 1.34 (s, 3H); ^{13}C NMR 75 MHz ($CDCl_3$) δ 170.3, 145.3, 110.4, 109.7, 101.7, 82.2, 78.6, 75.4, 73.6, 69.9, 67.1, 26.9, 26.3, 25.5, 25.1, 21.1; HRMS *m*/*z* for $C_{16}H_{24}O_7Na$ calcd 351.1420, found 351.1415.

*4.6.2. 1,6-Anhydro-[4,5;7,8]-di-O-isopropylidene-3-O-acetyl-2-deoxy-D-glycero-D-galactosept-1-enitol (**9a**).* Obtained as a clear colorless oil in 6% yield. R_f 0.45 (8:2 Hex/EtOAc); $[\alpha]_D$ +107.8 (*c* 0.16, $CHCl_3$); ^{1}H NMR 300 MHz ($CDCl_3$) δ 6.37 (d, *J*=7.1 Hz, 1H), 5.45 (dd, *J*=4.8 Hz, 1H), 4.7 (dd, *J*=7.4, 7.4 Hz, 1H), 4.55 (d, *J*=7.3 Hz, 1H), 4.48 (m, 1H), 4.28 (s,2H), 4.08 (m, 1H), 4.01 (m, 1H), 2.07 (s, 3H), 1.49 (s, 3H), 1.44 (s, 3H), 1.38 (s, 6H); ^{13}C NMR 75 MHz ($CDCl_3$) δ 169.5, 150.5, 110.1, 109.5, 98.9, 81.3, 76.3, 76.1, 74.2, 68.5, 66.8, 27.0, 26.2, 25.4, 25.2, 21.1; HRMS *m*/*z* for $C_{16}H_{24}O_7Na$ calcd 351.1420, found 351.1432.

*4.6.3. 1,6-Anhydro-[4,5]-O-isopropylidene-3-O-acetyl-2-deoxy-D-arabinosept-1-enitol (**8b**) and 1,6-anhydro-[4,5]-O-isopropylidene-3-O-acetyl-2-deoxy-D-ribosept-1-enitol (**9b**).* Isolated as an inseparable mixture of diastereomers in 44% yield as a clear colorless oil. R_f 0.6 (7:3 Hex/EtOAc); $[\alpha]_D$ −4.9 (*c* 0.14, $CHCl_3$); ^{1}H NMR 300 MHz ($CDCl_3$) δ 6.34 (d, *J*=7.4 Hz, 2H), 6.21 (dd, *J*=7.6, 1.5 Hz, 1H), 5.78 (ddd, *J*=7.9, 3.8, 1.5 Hz, 1H), 5.56 (dd, *J*=6.6, 2.6 Hz, 2H), 4.61 (dd, *J*=7.2, 6.8 Hz, 2H), 4.54–4.41 (m, 6H), 4.40–4.31 (m, 4H), 4.24 (m, 2H), 4.20 (m, 2H), 2.12 (s, 6H), 2.11 (s, 3H), 1.51 (s, 6H), 1.49 (s, 3H), 1.38 (s, 9H); ^{13}C NMR 100 MHz ($CDCl_3$) δ 170.1, 150.2, 147.5, 109.7, 109.5, 100.7, 98.4, 78.8, 78.1, 75.2, 75.1, 69.9, 69.4, 68.5, 67.6, 26.9, 26.3, 24.9, 24.8, 21.4, 21.2.

*4.6.4. 1,6-Anhydro-7-O-benzyl-[4,5]-O-isopropylidene-2-deoxy-D-altrosept-1-enitol (**8c**).* Obtained as a pale yellow oil in 19% yield. R_f 0.43 (7:3 Hex/EtOAc) $[\alpha]_D$ +68.1 (*c* 2.80, $CHCl_3$); ^{1}H NMR 400 MHz ($CDCl_3$) δ 7.40–7.27 (m, 5H), 6.50 (d, *J*=7.4 Hz, 1H), 4.90 (ddd, *J*=9.8,

4.8, 2.1 Hz, 1H), 4.75 (dd, *J*=8.6, 7.4 Hz, 1H), 4.67 (d, *J*=12.3 Hz, 1H), 4.60 (d, *J*=12.3 Hz, 1H), 4.45 (dd, *J*=9.9, 7.6 Hz, 1H), 4.27 (dd, *J*=7.5, 3.1 Hz, 1H), 4.22 (ddd, *J*=8.5, 2.7, 1.6 Hz, 1H), 3.83 (dd, *J*=10.9, 2.1 Hz, 1H), 3.73 (dd, *J*=11.0, 5.0 Hz, 1H), 1.53 (s, 3H), 1.40 (s, 3H); ^{13}C NMR 100 MHz ($CDCl_3$) δ 151.0, 138.3, 128.3, 127.6, 127.5, 108.1, 99.0, 77.9, 77.8, 74.8, 73.5, 70.2, 64.9, 26.3, 24.0; HRMS *m*/*z* for $C_{17}H_{22}NaO_5$ calcd 329.1359, found 329.1351.

*4.6.5. 1,6-Anhydro-7-O-benzyl-[4,5]-O-isopropylidene-3-O-acetyl-2-deoxy-D-allosept-1-enitol (**9c**).* Obtained as a pale yellow oil in 43% yield. R_f 0.68 (7:3 Hex/EtOAc); $[\alpha]_D$ +35.2 (*c* 0.86, $CHCl_3$); ^{1}H NMR 400 MHz ($CDCl_3$) δ 7.41–7.28 (m, 5H), 6.30 (dd, *J*=7.8, 2.3 Hz, 1H), 5.89 (ddd, *J*=10.2, 10.2 1.9 Hz, 1H), 4.67 (d, *J*=12.3 Hz, 1H), 4.60 (d, *J*=12.3 Hz, 1H), 4.52 (dd, *J*=10.5, 6.8 Hz, 2H), 4.38 (dd, *J*=10.1, 6.8 Hz, 1H), 4.25–4.35 (m, 2H), 3.83 (dd, *J*=10.9, 1.9 Hz, 1H), 3.72 (dd, *J*=10.9, 5.4 Hz, 1H), 2.14 (s, 3H), 1.45 (s, 3H), 1.37 (s, 3H); ^{13}C NMR 100 MHz ($CDCl_3$) δ 170.3, 146.1, 128.4, 127.6, 109.7, 102.9, 78.9, 78.0, 74.5, 73.5, 70.4, 70.1, 27.6, 25.4, 21.2; HRMS *m*/*z* for $C_{19}H_{24}O_6Na$ calcd 371.1471, found 371.1441.

*4.6.6. 1,6-Anhydro-7-O-tert-butyldiphenylsilyl-[4,5]-O-isopropylidene-3-O-acetyl-2-deox.y-D-altrosept-1-enitol (**8d**) and 1,6-anhydro-7-O-tert-butyldiphenylsilyl-[4,5]-O-isopropylidene-3-O-acetyl-2-deoxy-D-allosept-1-enitol (**9d**).* This material was obtained as clear colorless oil in 56% yield as a 3:1 mixture of diastereomers. R_f 0.5 (8:2 Hex/EtOAc); ^{1}H NMR 300 MHz ($CDCl_3$) δ 7.77–7.69 (m,16H), 7.47–7.35 (m, 24H), 6.47 (d, *J*=7.3 Hz, 1H), 6.28 (dd, *J*=7.4, 2.2, Hz, 3H), 5.85 (ddd, *J*=10.2, 1.8, 1.8 Hz, 3H), 5.29 (dd, *J*=9.5, 3.1 Hz, 1H), 4.78 (dd, *J*=8.6, 7.3 Hz, 1H), 4.54 (m, 4H), 4.37 (dd, *J*=10.2, 6.9 Hz, 3H), 4.30 (dd, *J*=7.6, 1.6 Hz, 3H), 4.16 (ddd, *J*=7.2, 5.3, 2.1 Hz 1H), 4.05 (dd, *J*=11.5, 1.6 Hz, 1H), 4.00–3.95 (m, 3H), 3.87 (dd, *J*=11.3, 5.2 Hz, 1H), 2.13 (s, 9H), 2.06 (s,3H), 1.45 (s, 3H), 1.43 (s, 9H), 1.35 (s, 12H), 1.09 (s, 9H), 1.08 (s, 27H); ^{13}C NMR 75 MHz ($CDCl_3$) δ 170.3, 170.1, 152.0, 146.3, 135.7, 135.7, 133.5, 133.4, 129.7, 129.6, 127.7, 127.6, 109.6, 108.9, 102.7, 100.0, 97.9, 79.9, 79.4, 78.9, 74.5, 74.3, 70.4, 67.6, 64.6, 64.5, 27.6, 26.8, 26.4, 25.4, 24.8, 21.5, 21.2, 19.4 (2); HRMS *m*/*z* for $C_{28}H_{36}O_6SiNa$ calcd 519.2179, found 519.2159.

4.7. (1*R*)-*O*-Methyl-(5*R*,6*R*-[2,2]-dimethyl-1,3-dioxolo)-oxepan-4-one (10)

Compound **7b** (0.18 g, 0.998 mmol) was dissolved in MeOH (15 mL) and solid NaOMe (1.5 mg, 0.0278 mmol) was added to the reaction. The mixture was stirred at rt for 30 h then concentrated in vacuo. The residue was purified by column chromatography (3:1 Hex/EtOAc) to yield 105 mg (49%) of **10**. R_f 0.37 (7:3 Hex/EtOAc); $[\alpha]_D$ −117.7 (*c* 4.29, $CHCl_3$); ^{1}H NMR 300 MHz ($CDCl_3$) δ 4.76 (dd, *J*=7.1, 5.0 Hz, 1H), 4.59 (d, *J*=7.6 Hz, 1H,), 4.38 (ddd, *J*=7.5, 2.5, 1.5 Hz, 1H), 4.15 (dd,, *J*=14.6, 1.1 Hz, 1H), 3.91 (dd, *J*=14.6, 2.9 Hz, 1H), 3.38 (s, 3H), 2.90 (dd, *J*=12.3, 5.0 Hz, 2H), 2.80 (dd, *J*=12.2, 7.1 Hz, 1H), 1.57 (s, 3H), 1.40 (s, 3H); ^{13}C NMR 75 MHz ($CDCl_3$) δ 201.2, 110.8, 97.2, 83.1, 74.6, 58.5, 55.6, 43.5, 27.0, 25.6; HRMS *m*/*z* for $C_{10}H_{16}O_5Na$ calcd 239.0895, found 239.0902.

4.8. Thiophenyl oxepanones 11 and 12

Compound **7b** (0.18 g, 0.998 mmol) was dissolved in dry THF (25 mL) and cooled to 0 °C and Cs_2CO_3 (0.33 g, 0.998 mmol) was added. To this mixture was added thiophenol (0.409 mL, 3.99 mmol) under N_2. The solution was stirred at 0 °C for 30 min and the reaction was then quenched with H_2O (20 mL) and extracted with DCM (3×15 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. The crude material was purified by column chromatography (3:1 Hex/EtOAc) yielding **8** and **9** in a combined yield of 0.189 g (64%, 1:1 dr).

*4.8.1. (1S)-S-Phenyl-(5R,6R-[2,2]-dimethyl-1,3-dioxolo)-oxepan-4-one (**11**).* Obtained as a clear colorless oil. R_f 0.52 (7:3 Hex/EtOAc); $[\alpha]_D$ −406.9 (*c* 0.24, $CHCl_3$); ^{1}H NMR 400 MHz ($CDCl_3$) δ 7.52–7.47 (m, 2H), 7.36–7.26 (m, 3H), 5.46 (dd, *J*=10.1, 5.4 Hz, 1H), 4.65 (d, *J*=7.5 Hz, 1H), 4.47 (m, 2H), 4.01 (dd, *J*=15.1, 3.5 Hz, 1H), 3.03 (dd, *J*=12.2, 5.3 Hz, 1H), 2.93 (dd, *J*=12.0, 10.1 Hz, 1H), 1.57 (s, 3H), 1.42 (s, 3H); ^{13}C NMR 100 MHz ($CDCl_3$) δ 201.6, 133.5, 131.9, 129.2, 128.0, 110.9, 83.0, 82.9, 74.2, 60.7, 43.4, 27.1, 25.6. HRMS *m*/*z* for $C_{15}H_{18}O_4SNa$ calcd 317.0824, found 317.0839.

*4.8.2. (1R)-S-phenyl-(5R,6R-[2,2]-dimethyl-1,3-dioxolo)-oxepan-4-one (**12**).* Obtained as a white solid. Mp 98.5–101.0 °C; R_f 0.69 (7:3 Hex/EtOAc); $[\alpha]_D$ +234.2 (*c* 0.49, $CHCl_3$); ^{1}H NMR 400 MHz ($CDCl_3$) δ 7.58–7.42 (m, 2H), 7.38–7.26 (m, 3H), 5.17 (dd, *J*=8.9, 4.2 Hz, 1H), 4.65 (d, *J*=10.2, 6.9 Hz, 3H), 4.40 (ddd, *J*=7.3, 7.3, 3.1 Hz, 1H), 4.20 (dd, *J*=13.5, 7.2 Hz, 1H), 3.54 (dd, *J*=13.5, 3.0 Hz, 1H), 3.43 (dd, *J*=11.6, 8.9 Hz, 1H), 2.87 (ddd, *J*=11.7, 4.1, 1.0 Hz, 1H), 1.61 (s, 3H), 1.40 (s, 3H); ^{13}C NMR 100 MHz ($CDCl_3$) δ 203.1, 133.3, 132.6, 130.7, 129.3, 129.2, 128.2, 112.0, 85.0, 82.9, 73.8, 66.3, 45.8, 27.2, 25.4; HRMS *m*/*z* for $C_{15}H_{18}O_4SNa$ calcd 317.0824, found 317.0820.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.07.041.

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