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Direct assembly of multiply oxygenated carbon chains by decarbonylative radical–radical coupling reactions

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Pentoses and hexoses contain more than three oxygen-bearing stereocentres and are ideal starting materials for the synthesis of multiply oxygenated natural products such as sagittamide D, maitotoxin and hikizimycin. Here we demonstrate new radical–radical homocoupling reactions of sugar derivatives with minimal perturbation of their chiral centres. The radical exchange procedure using Et_3B/O_2 converted sugar-derived α-alkoxyacyl tellurides into α-alkoxy radicals via decarbonylation and rapidly dimerized the monomeric radicals. The robustness of this process was demonstrated by a single-step preparation of 12 stereochemically diverse dimers with 6–10 secondary hydroxy groups, including the C5–C10 stereohexad of sagittamide D and the enantiomer of the C51–C60 stereodecad of maitotoxin. Furthermore, the optimally convergent radical–radical cross-coupling reaction achieved a one-step assembly of the protected C1–C11 oxygenated carbon chain of the anthelmintic hikizimycin. These exceptionally efficient homo- and heterocoupling methods together provide a powerful strategy for the expedited total synthesis of contiguously hydroxylated natural products.

Contiguously hydroxylated unbranched carbon chains are embedded in a number of naturally occurring secondary metabolites with pharmacologically important bioactivities[1–4]. As illustrated in Fig. 1, the structure of sagittamide D (ref. 5), a marine natural product, contains a C5–C10 stereohexad of six contiguous acetoxy groups. Maitotoxin (neurotoxin) and hikizimycin (anthelmintic) embody even more complex structural features. While the C48–C60 subunit of maitotoxin possesses eight ethereal oxygen functional groups and five hydroxy groups[6], the C1–C11 chain of hikizimycin is decorated by nine oxygen-based and two nitrogen-based functionalities[7–9]. Chemists have generally tackled the synthesis of these densely oxygenated architectures by employing multiple steps of carbon elongations and functional-group transformations[10–15].

As naturally abundant monosaccharides have continuous networks of three (for example, D-ribose) or four (for example, D-glucose, D-galactose and D-mannose) secondary hydroxy groups, they constitute a rich reservoir of oxygenated carbon sources[16–19]. In addition, recent advances in asymmetric synthesis allow for the expeditious *de novo* preparation of a series of scarce or artificial monosaccharide structures, which include the mirror images of common D-monosaccharides[20–22]. Accordingly, numerous stereochemically distinct pentoses and hexoses are commercially or synthetically available, and they serve as extremely versatile starting materials for synthesizing polyol natural products. If intermolecular $C(sp^3)$–$C(sp^3)$ bond formation between two monosaccharides can be accomplished with a full utilization of their chiral information, this should be most desirable in realizing a shorter synthetic route to the polyhydroxylated targets. Nevertheless, such methodologies are relatively unexplored[23,24].

Radical–radical coupling reactions of α-oxygenated carbon radicals are a potentially powerful synthetic strategy for efficiently assembling the highly oxygenated carbon chains (Fig. 2). Even the simple dimerization of monomeric radical **A**, in a single step, doubles the number of secondary hydroxy groups by yielding polyol **2**. In previous studies[25–32], a key radical intermediate **A** or **A′** was typically generated via an oxidative or reductive reaction (Fig. 2b). While anodic oxidation of carboxylic acid **3**[25–27] leads to **A** with the expulsion of CO_2, the reductions of the C–X bond of O,X-acetal **E**[28–30] and the C=O bond of aldehyde **F**[31,32] produce **A** and **A′**, respectively. These important methods, however, have major drawbacks. For example, further electron transfer from **A** to an electrode and from a low valent metal (MX_n) to **A′** would abolish the radicals and would result in a nucleophile addition to the resultant α-alkoxy cation and β-elimination of R^2O^- from the α-alkoxy anion, respectively. On the other hand, the C–X bond of **E** is intrinsically unstable because of its facile heterolysis by electron donation from the oxygen lone pair. To overcome these limitations, we aimed to design more chemoselective reaction conditions and more stable radical precursors to develop a generic radical–radical $C(sp^3)$–$C(sp^3)$ coupling method.

In 2015, we reported that α-alkoxy carbon radical **A** is rapidly formed from α-alkoxyacyl telluride **1** in the presence of Et_3B/O_2 (ref. 33), and is smoothly added to electron-deficient double bonds[34–36]. The first part of this transformation involves (1) the generation of an Et radical from Et_3B and O_2, (2) a radical exchange reaction from the Et radical to the corresponding acyl radical **B** through the C–Te homolysis of **1** (ref. 37) and (3) decarbonylation from **B** to **A** (Fig. 2a). With the chemical stability of the non-acetal structure **1** and the high chemoselectivity of the radical exchange reaction, we decided to exploit **1** as a substrate for radical dimerization. We anticipated that the favourable orbital interaction between the σ^* bond of **B** with the adjacent oxygen lone pair would facilitate the C–CO scission to form **A**[38,39], and the stable radical **A** would be more concentrated than precursor **B** or the unstable Et radical. Thus, the desired **2** should be produced preferentially over the other potential coupling adducts **C** and **D**. Herein we report the development of efficient Et_3B/O_2-promoted radical–radical coupling reactions of α-alkoxyacyl tellurides **1a**–**1l**, derived from the common pentoses and hexoses. A broad applicability of the dimerization of the monosaccharide derivatives was demonstrated by a single-step preparation of the stereochemically diverse

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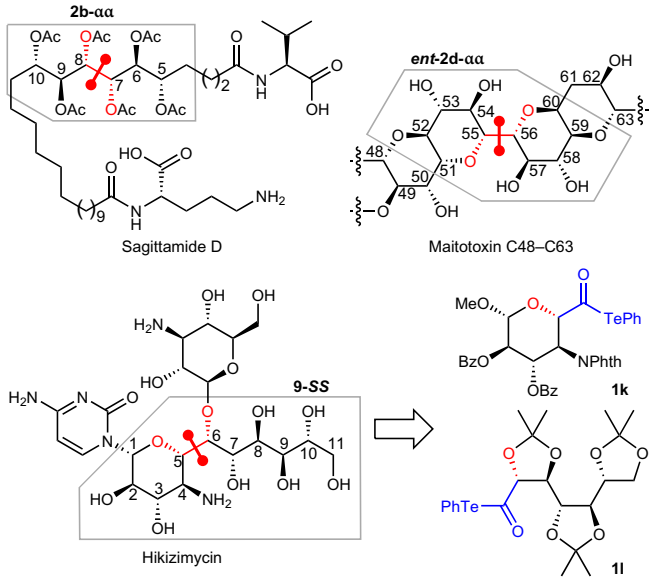


Figure 1 | Representative examples of multiply oxygenated natural products and retrosynthetic analysis of hikizimycin. Hexoses and pentoses make up the cores of many important bioactive secondary metabolites. Typically, these structures have been made through sequential elongation or oxidation of carbon chains, although the ability to couple the constituent sugars directly would greatly streamline the preparation of these complex, highly oxidized molecules. The substructures of sagittamide D (C5–C10), maitotoxin (C51–C60) and hikizimycin highlighted in the boxes correspond to the structures of **2b-αα**, ***ent*-2d-αα** and **9-*SS***, respectively.

12 dimers **2a**-**2l**, including the C5–C10 stereohexad of sagittamide D (**2b-αα**) and the enantiomer of the C51–C60 stereodecad of maitotoxin (**2d-αα**) (Fig. 1). Furthermore, radical–radical cross-coupling between the structurally distinct monomers **1k** and **1l** was accomplished to deliver directly the protected C1–C11 oxygenated carbon chain of hikizimycin (**9-*SS***).

Results and discussion

The 12 structurally varied carboxylic acid derivatives **3a**–**3l** were selected as precursors of the corresponding α-alkoxyacyl tellurides to evaluate systematically the effects of the three-dimensional (3D) structures on the stereochemical outcome of radical dimerization (Fig. 3). Monosaccharide carboxylic acids **3a**/**3b**, **3c**/**3d**, **3e**/**3f** and **3g**/**3h** possess the stereochemistry of D-ribose, D-glucose, D-galactose and D-mannose, respectively, and are pairs of the C1 epimers, whereas **3i** and **3j** are differentially protected linear analogues of **3g** and **3h**. The ten compounds **3a**–**3j** were readily prepared from known materials in protocols of one to three steps. The structures of **3k** and **3l** correspond to the C1–C5 and C6–C11 moieties of hikizimycin, and were synthesized from the D-galactose derivative **4** in five steps and the D-mannose derivative **7** in four steps, respectively. After site-selective bis-benzoylation of **4**, triflation of the remaining axially oriented hydroxy groups of **5** was followed by nucleophilic displacement, introducing the C4–NPhth group (Phth, phthaloyl) of **6**. Acidic deprotection of the C6–OH of **6** and subsequent TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl) oxidation[40] then gave rise to **3k**. On the other hand, carbon extension at C1 from **7** and subsequent protective-group manipulation afforded the known **8** (ref. 41), the dithioacetal group of which was converted into the carboxylic acid of **3l** by NBS (*N*-bromosuccinimide)-promoted hydrolysis and $NaClO_2$ oxidation of the resulting aldehyde.

The 12 sugar-derived acids **3a**–**3l** thus synthesized were in turn converted into α-alkoxyacyl tellurides **1a**–**1l** in one pot (Table 1)[34–36]. Specifically, D-ribose carboxylic acid **3a** was condensed with *i*-butyl chloroformate to form the activated ester, which was treated *in situ* with PhTeNa, prepared from $(PhTe)_2$ and $NaBH_4$, to provide α-alkoxyacyl telluride **1a** in 85% yield. Other tellurides, **1b**–**1l**, were obtained in the same manner, and all of the products were stable to air, fluorescent light and silica gel, and thereby function as reliable intermediates for subsequent dimerization reactions. Notably, the benzoyl (**1a**–**1i** and **1k**), acetonide (**1a**, **1b**, **1j** and **1l**), methylene acetal (**1i**), TBDPS (*tert*-butyldiphenylsilyl) (**1j**) and phthalate (**1k**) groups were all tolerated under these conditions.

We first investigated the efficacy and selectivity of the crucial intermolecular C(sp^3)–C(sp^3) bond formation of the most structurally simple pentoses **1a** and **1b** among the 12 α-alkoxyacyl tellurides **1a**–**1l** (Table 1). When **1a** was treated with Et_3B (5 equiv.) in benzene (0.2 M) under air at ambient temperature for 20 minutes, dimers **2a-αα**, **2a-αβ** and **2a-ββ** with the eight contiguous oxygen functionalities were produced in a 68% combined yield. The stereochemical information at the α-alkoxy carbon was lost on the formation of radical **Aa** from **1a** via decarbonylation, and in turn redefined when dimers **2a-αα**, **2a-αβ** and **2a-ββ** were generated. Comparison of the observed ratio of **2a-αα**/**2a-αβ**/**2a-ββ** (35:55:10) with the statistical distribution (25:50:25) revealed a modest α selectivity. Intriguingly, dimerization of the differentially protected pentose **1b** under the same conditions exhibited a higher α selectivity than that of **1a**, which led to **2b-αα**, **2b-αβ** and **2b-ββ** in a 53:41:6 ratio (61% combined yield).

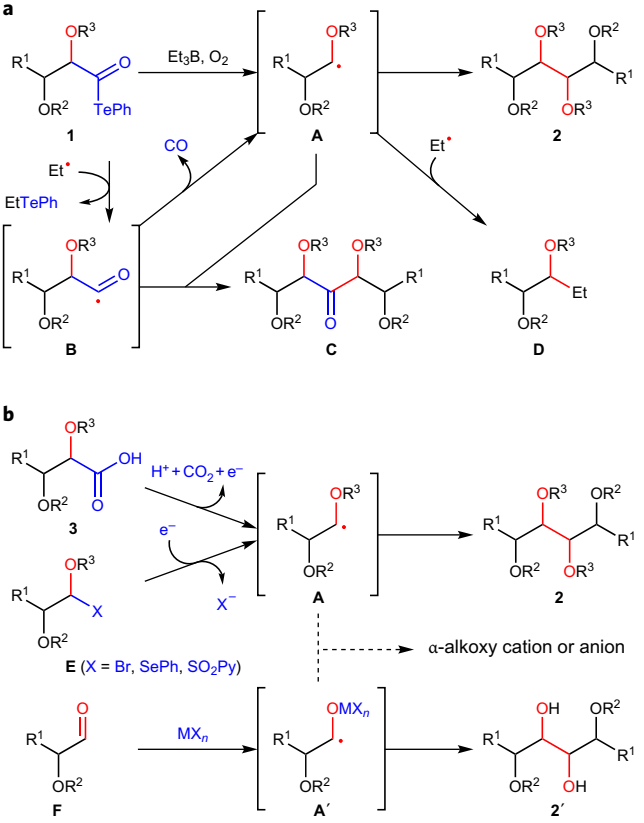


Figure 2 | Radical–radical coupling strategies for the synthesis of contiguously substituted polyol structures. a, Et_3B/O_2-mediated decarbonylative radical exchange reaction of α-alkoxyacyl telluride **1** in this study. Decarbonylation of acyl radical **B** gives α-alkoxy radical **A**, which dimerizes to form **2**. Compounds **C** and **D** are potential by-products. **b**, Oxidative decarboxylative reaction of α-alkoxycarboxylic acid **3**, or the reductive reactions of O,X-acetal **E** and aldehyde **F** in previous studies[25–32]. The formation of an α-alkoxy cation or anion is a possible undesired pathway. Py, 2-pyridyl.

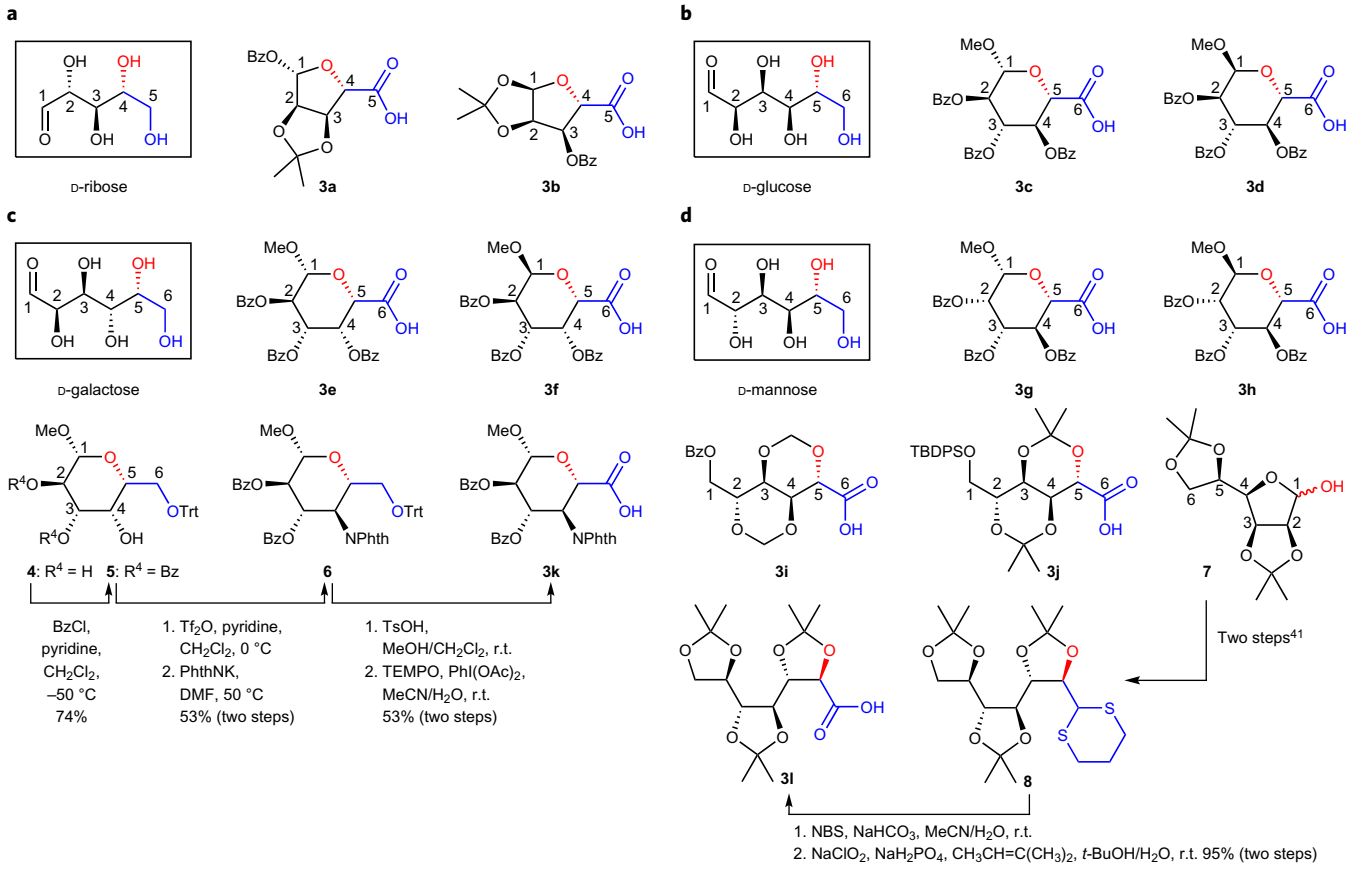


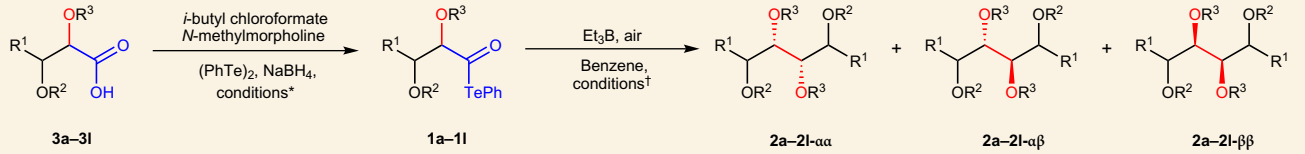
Figure 3 | Structures of the four D-sugars used in this study and their carboxylic acid derivatives 3a–3j, and synthesis of 3k and 3l from 4 and 7. **a**, Compounds **3a** and **3b** possess the stereochemistry of D-ribose. **b**, Compounds **3c** and **3d** possess the stereochemistry of D-glucose. **c**, Compounds **3e** and **3f** possess the stereochemistry of D-galactose. Compound **3k** was prepared from the D-galactose derivative **4**. **d**, Compounds **3g**–**3j** possess the stereochemistry of D-mannose. Compound **3l** was prepared from the D-mannose derivative **7**. Tf_2O, trifluoromethanesulfonic anhydride; Trt, triphenylmethyl; TsOH, *p*-toluenesulfonic acid; r.t., room temperature.

We next applied the dimerization method to the hexose derivatives **1c**–**1h**, which share an identical planar structure, yet have distinct stereochemistries. Acyl tellurides **1c**–**1h** all expelled carbon monoxide in the presence of Et_3B and O_2, and consistently afforded the corresponding dimers **2c**–**2h** with the ten oxygen-based functionalities. Interestingly, the diastereomer ratios of **2c**–**2h** were varied. While D-glucose derivatives **1c** and **1d** were converted into **2c** (53%) and **2d** (61%) as 27:53:20 and 47:44:9 mixtures of the αα/αβ/ββ diastereomers, respectively, **2e** (47%, 0:42:58) and **2f** (55%, 10:51:39) were obtained from D-galactose derivatives **1e** and **1f**, respectively. Alternatively, the radical coupling of D-mannose analogues **1g** and **1h** led to dimers **2g** (46%, 16:49:35) and **2h** (60%, 30:54:16).

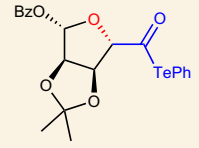
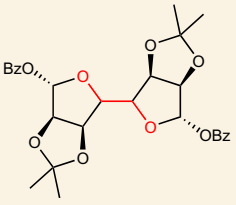
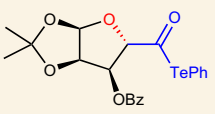
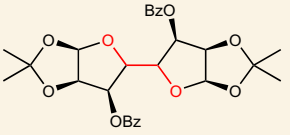
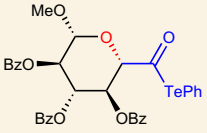
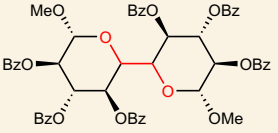
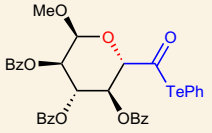
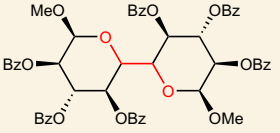
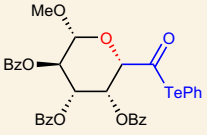
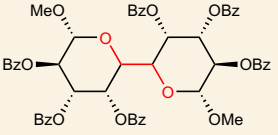
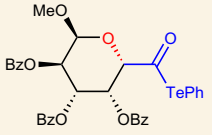
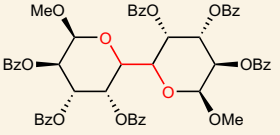
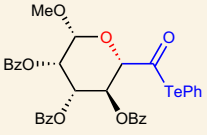
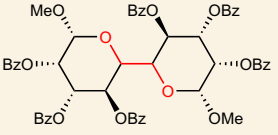
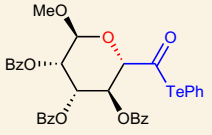
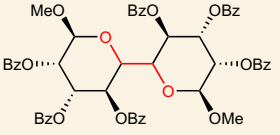
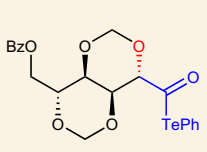
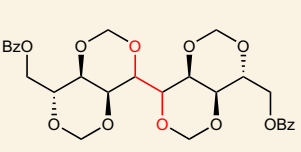
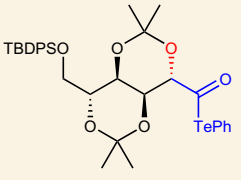
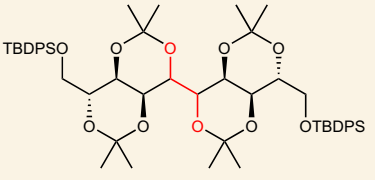
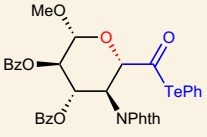
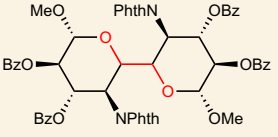
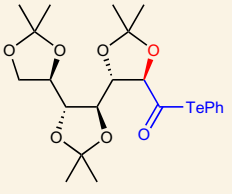
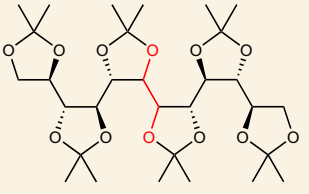
The linear analogues **1i** and **1j** of D-mannose and the hikizimycin substructures **1k** and **1l** were then subjected to the reagent combination of Et_3B and O_2. The multiply functionalized long carbon chains **2i**–**2l** were readily constructed via the decarbonylative $C(sp^3)$–$C(sp^3)$ bond formation, and the αα-, αβ- and ββ-isomer ratios were established separately as 31:54:15 (**2i**, 54%), 40:60:0 (**2j**, 71%), 17:68:15 (**2k**, 60%) and 6:43:51 (**2l**, 56%). Rapid decarbonylation and radical–radical coupling between the resultant α-alkoxy radicals **A** smoothly occurred in all the dimerization reactions of **1a**–**1l**, and effectively suppressed the generation of the potential by-products **C** and **D** (Fig. 2). Moreover, oxidation of the α-alkoxy radical **A** to the oxocarbenium cation or β-elimination of the oxygen (**1a**–**1j** and **1l**) and amino (**1k**) functionalities was not observed, which underlined the advantageous features of the radical exchange conditions over the oxidative or reductive radical reactions. Despite the modest stereoselectivity, single-step preparation of the variously adorned dimers **2a**–**2l** with the eight or ten contiguous stereocentres clearly showed the exceptional efficacy of the present method for synthesizing the densely functionalized structures. In fact, the C5–C10 portion of sagittamide D (**2b-αα**) and the enantiomer of the C51–C60 substructure of maitotoxin (**2d-αα**) were immediately constructed and isolated as the major isomers in 32 and 29% yields, respectively, from simple carbohydrate derivatives.

Radical coupling reactions of **1b**, **1d**, **1e**, **1g**, **1j** and **1l** displayed a higher stereoselectivity than those of the other six substrates **1a**, **1c**, **1f**, **1h**, **1i** and **1k**. The observed stereochemical outcome could be explained by a combination of favourable stereoelectronic and unfavourable steric interactions (Fig. 4). The 3D structures of the radical intermediates **Ab**, **Ad**, **Ae**, **Ag**, **Aj** and **Al** represent the assumed conformations, which are stabilized by orbital interactions of the singly occupied molecular orbital with the *n*-orbital of the α-oxygen atom and/or with the σ^* orbital of the coplanar β-C–OBz bond (shown in red in Fig. 4)[42–48]. The sterically cumbersome groups (highlighted in grey in Fig. 4) block the approach of the coupling partner from the same face, which results in α selectivity for **Ab**, **Ad** and **Aj** and β selectivity for **Ae**, **Ag** and **Al**. As the governing stereoelectronic factors were comparable among the 12 α-alkoxy radicals **Aa**–**Al**, the lower stereoselectivity from **1a**, **1c**, **1f**, **1h**, **1i** and **1k** would be caused by the lack of sterically blocking axial substituents (**Ac**, **Ai** and **Ak**) or the counteracting steric effects of the two axially oriented oxygen-based functional groups (**Aa**, **Af** and **Ah**) on the opposite faces (Supplementary Section 7 gives more details).

Table 1 | Preparation of acyl tellurides 1a–1l and their radical–radical homocoupling reactions.



3a–3l 1a–1l 2a–2l-αα 2a–2l-αβ 2a–2l-ββ

Acyl telluride (yield)	Dimer (yield, αα:αβ:ββ)	Acyl telluride (yield)	Dimer (yield, αα:αβ:ββ)
 **1a** (85%, from **3a**)	 **2a** (68%, 35:55:10)	 **1b** (76%, from **3b**)	 **2b** (61%, 53:41:6)
 **1c** (76%, from **3c**)	 **2c** (53%, 27:53:20)	 **1d** (69%, from **3d**)	 **2d** (61%, 47:44:9)
 **1e** (67%, from **3e**)	 **2e** (47%, 0:42:58)	 **1f** (80%, from **3f**)	 **2f** (55%, 10:51:39)
 **1g** (67%, from **3g**)	 **2g** (46%, 16:49:35)	 **1h** (66%, from **3h**)	 **2h** (60%, 30:54:16)
 **1i** (58%, from **3i**)	 **2i** (54%, 31:54:15)	 **1j** (71%, from **3j**)	 **2j** (71%, 40:60:0)
 **1k** (56%, from **3k**)	 **2k** (60%, 17:68:15)‡	 **1l** (78%, from **3l**)	 **2l** (56%, 6:43:51)

*Reagents and conditions: *i*-butyl chloroformate (1.2 equiv.), *N*-methylmorpholine (1.2–1.5 equiv.), THF (0.2 M), 0 °C, 30 min; $(PhTe)_2$ (1 equiv.), $NaBH_4$ (3 equiv.), THF/MeOH (10:1, 0.2 M), 0 °C, 30 min; r.t., 30 min. ‡Et_3B (5 equiv.), benzene (0.2 M), r.t., 20 min, under air. ‡Et_3B (3 equiv.) was used.

With the establishment of the efficient homocoupling procedure of **1a**–**1l**, we turned our efforts towards the elongation of the polyhydroxylated carbon chain of hikizimycin from the different monomers **1k** and **1l** (Fig. 5). The cross-coupling reaction of the two components significantly increased the synthetic complexity compared with their dimerizations. The one reaction between **1k** and **1l** would produce six homo-coupled (**2k-αα**, **2k-αβ**, **2k-ββ**, **2l-αα**, **2l-αβ** and **2l-ββ**) and four cross-coupled (**9-*SS***, **9-*RS***, **9-*SR*** and **9-*RR***) adducts, and only **9-*SS*** among the ten compounds corresponds to the hikizimycin structure. We decided to address this unconventional and formidable problem because the single-step construction of **9-*SS*** would ensure the optimal synthetic convergence[49]. When 2 equiv. of **1k** are used with **1l**, adducts **2k**, **9** and **2l** should theoretically form in a 4:4:1 ratio, and a 25:25:25:25 distribution of **9-*SS***, **9-*RS***, **9-*SR*** and **9-*RR*** is expected if the radical intermediates **Al** and **Ak** have the same reactivity and exhibit no stereoselectivity of their couplings. As **1l** would be consumed twice as much on the formation of its dimer **2l** relative to formation of **9**,

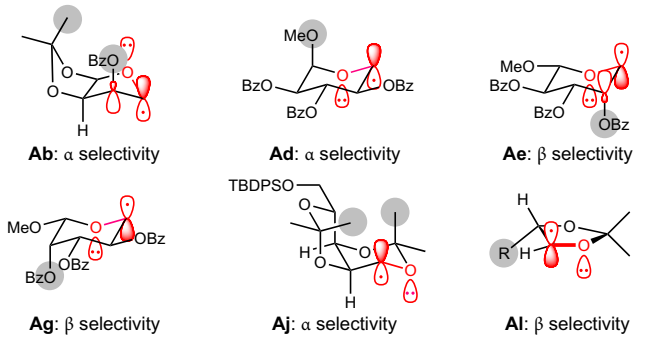


Figure 4 | Presumed conformations of the representative α-alkoxy radicals. The varying stereoselectivity of the substrates studied here can be rationalized by examining the steric environment of the incumbent radical species. The conformations are stabilized by orbital interactions of the singly occupied molecular orbital with the *n* orbital of the oxygen atom and/or the σ^* orbital of the C–O bond (shown in red). The potential stereocontrolling bulky substituents are indicated in grey in the structures.

the maximum yield of **9** from **1l** would be 67% (=4/(2 × 1 + 4) × 100%), where only one-quarter corresponds to the desired **9-*SS*** (17%). In effecting this intricate reaction, an excess of Et_3B (15 equiv.) was utilized in benzene/CH_2Cl_2 under air at room temperature in the presence of **1k** (2 equiv.) and **1l**. As a result, **9-*SS*** was isolated as the most-abundant compound (17%), together with the cross-coupled diastereomers **9-*RS*** (7.8%), **9-*SR*** (5.2%) and **9-*RR*** (1.7%), and the dimers **2k-αα**, **2k-αβ** and **2k-ββ** (34%) and **2l-αα**, **2l-αβ** and **2l-ββ** (trace). The selective formation of **9-*SS*** and **9-*RS*** over **9-*SR*** and **9-*RR*** (**9-*SS*/9-*RS*/9-*SR*/9-*RR*** = 53:25:16:6) was attributable to the strong stereochemical bias of radical **Al** (Fig. 4 and Table 1). The ratio between **9-*SS*** and **9-*RS*** indicated a higher α-stereoselectivity of **Ak** compared with its dimerization (Table 1). As a result of these two favourable stereoselectivities, the single-step construction of **9-*SS*** reached a statistically maximum yield (17%), which corroborates the efficiency of this radical–radical cross-coupling reaction. Overall, the densely oxygenated unbranched carbon chain **9-*SS*** was constructed in only seven steps from the commercially available protected D-galactose **4**.

To confirm its absolute structure, **9-*SS*** was derivatized into the known methyl peracetyl hikosaminide (**10**), which was reported to come from natural hikizimycin by six functional-group manipulations (Fig. 5)[7,8]. Removal of the benzoyl, phthaloyl and acetonide protective groups from **9-*SS*** was realized by sequential treatment with NaOMe/MeOH, HCl/MeOH and N_2H_4/MeOH, respectively, giving rise to the deprotected compound. Finally, the amino octanol was peracetylated with Ac_2O in pyridine to deliver **10** in 65% overall yield as a mixture of the acetalic C1-epimers. Analytical data of the fully synthetic **10**, including the specific rotation and the ^{1}H-NMR data, matched those of the hikizimycin-derived **10**[12], and thereby proved the integrity of all ten contiguous stereocentres within the structure of **10**.

Conclusion

In summary, we devised new radical–radical homocoupling reactions of the sugar-derived α-alkoxyacyl tellurides **1a**–**1l**, and realized a one-step construction of the 12 polyol structures **2a**–**2l** with the 6–10 secondary hydroxy groups under simple and mild conditions. The radical exchange procedure using Et_3B/O_2 at room temperature converted **1a**–**1l** into the corresponding α-alkoxy radicals **Aa**–**Al** through the expulsion of CO, and readily dimerized **Aa**–**Al** into **2a**–**2l**. On the C(sp^3)–C(sp^3) bond formation, the combination of stereo- and stereoelectronic factors of **Aa**–**Al** controlled the generation of two new stereocentres of the diverse polyhydroxylated carbon chains of **2a**–**2l**. The large substructures of sagittamide D (**2b-αα**) and enantiomeric maitotoxin (**2d-αα**) were prepared from simple components, which exemplifies the remarkable utility of the present dimerization. The homocoupling methodology was then successfully extended to an optimally convergent radical–radical cross-coupling reaction. Among the possible six homo- and four heterocoupling adducts, the hikizimycin structure **9-*SS*** with nine correct contiguous stereocentres was selectively built from monomers **1k** and **1l**. These 12 homo- and one cross-coupling reactions enabled the one-step construction of contiguously substituted polyol structures, which were prepared by multiple carbon extension and functional-group transformations. As a result of the excellent efficiency together with the high availability of the natural and artificial monosaccharide derivatives, this unique and powerful radical coupling method can serve as a novel strategy for

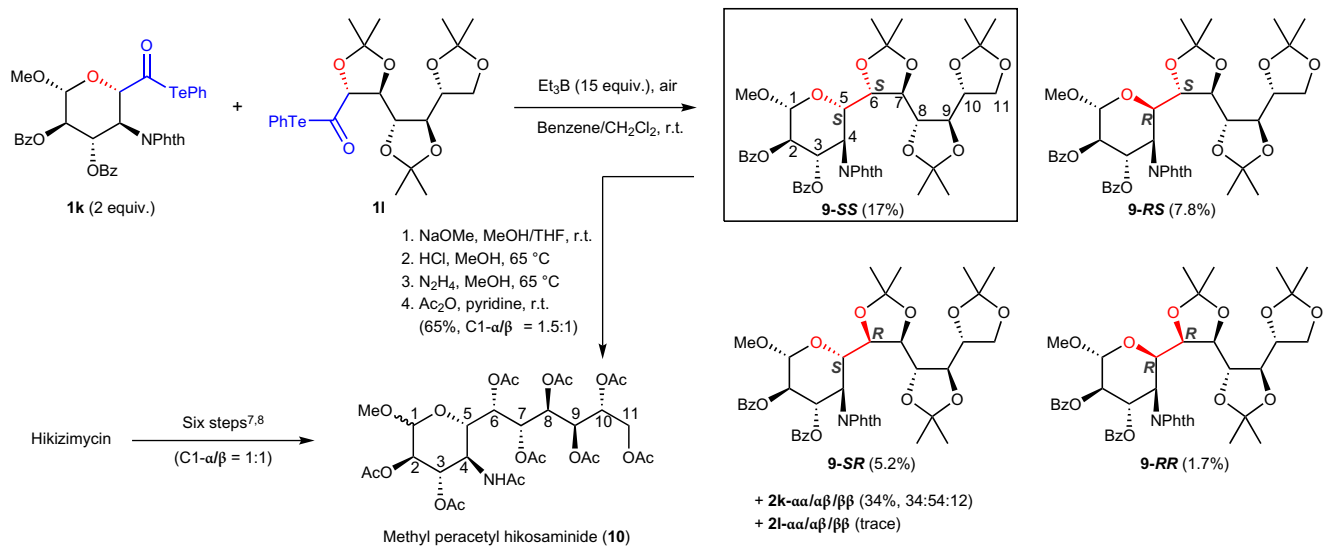


Figure 5 | Radical–radical cross-coupling reaction for the synthesis of the hikizimycin carbon chain 9-*SS*. The statistical quantitative yield and diastereomer ratio of **9-*SS*/*RS*/*SR*/*RR*** are 67% and 25:25:25:25, respectively. The obtained yield and diastereomer ratio of **9-*SS*/*RS*/*SR*/*RR*** were 32% and 53:25:16:6, respectively. To confirm the stereostructure, the major isomer **9-*SS*** was converted into methyl peracetyl hikosaminide (**10**), which was previously derivatized from hikizimycin[7,8].

streamlining the synthesis of diverse polyoxygenated carbon chains that are frequently found in complex bioactive natural products.

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Author contributions

K.M., M.N. and M.I. conceived and designed the study. K.M. and M.N. performed the syntheses and M.N. and M.I. co-wrote the paper.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to M.I.

Competing financial interests

The authors declare no competing financial interests.