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Synthesis of an Acyclic C1–C11 Fragment of Peloruside B

Qin Zang,[a] Shivali Gulab,[b] Bridget L. Stocker,[b,c] Sylvia Baars,[b] and John O. Hoberg*[a]

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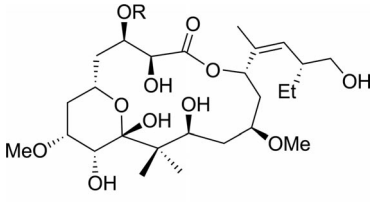
The synthesis of a C1 reduced form of the C1–C11 fragment of peloruside B has been achieved in 15 synthetic steps. The strategy involved the use of D-tartaric acid to set the absolute stereochemistry and a 1,5-*anti* Mukiayama aldol reaction. Analog synthesis of C8–C11 is also reported, which enables changes at the C10 position of peloruside B to be made. The synthesis of the fragment concludes with C1 in the protected alcohol state rather than the natural ester.

Introduction

Peloruside A[1] (**1**, Figure 1) is a potent antimitotic macrolide isolated from the New Zealand marine sponge *Mycale hentscheli* with cytotoxicity to murine leukemic cell lines at 18 nM. In the cell cycle, peloruside A has been shown to prevent cell division by promoting microtubule polymerization via accumulation in the G_2/M phase of mitosis,[2] similar to paclitaxel.[3] Furthermore, peloruside A has been shown to have a microtubule binding site that is different from paclitaxel and similar to laulimalide,[4,5] and unlike paclitaxel, peloruside A does not induce production of proinflammatory mediators in murine macrophages.[6] Recently, a natural congener of peloruside A, peloruside B (**2**, Figure 1), was reported, along with its activity and total synthesis.[7] The bioactivity of peloruside B was reported to be comparable to that of peloruside A, thus making it an equally attractive synthetic target.



R = Me, Peloruside A (**1**)
R = H, Peloruside B (**2**)

Figure 1. Peloruside A and B.

The potential and attraction of the peloruside family as anticancer agents can be seen with the entrance of peloruside A into preclinical trials,[8,9] numerous partial syntheses,[10] and the five reported total syntheses of peloruside A. De Brabander[11] established the correct absolute stereochemistry with the first total synthesis of unnatural (–)-peloruside A, which was followed by three additional total syntheses of the natural (+)-isomer[12–14] and a (–)-2-*epi* synthesis.[15] Furthermore, the 16-membered macrolide of the peloruside family with the 10 stereochemical centers in which the hydroxy and the heteroatom-containing side chain are crucial elements, make for a challenging target. Additionally, the importance of the pyranoside moiety of peloruside A has been shown to be critical for activity, as $NaBH_4$ reduction of peloruside A to the acyclic diol resulted in a 30-fold less-active compound when compared to the parent compound.[16] Furthermore, "the dimethyl moiety has hydrophobic interactions with the Arg308 of the binding site, which plays a dual role in stabilizing the interaction of peloruside A with β-tubulin".[17] As a result of these observations, we became interested in the development of a convergent aldol-based synthesis of peloruside B, which would enable modifications to the *gem*-dimethyl position while keeping the crucial pyranose region of the macrolide intact.

Our strategy relies on two key aldol reactions between carbon atoms 7–8 and 11–12, as illustrated in Scheme 1. The coupling of aldehyde **3** and enol ether **4** involves a chelation-controlled Mukaiyama aldol reaction to set the stereochemistry at C7 and C8, and this is the subject of this paper. The second critical aldol involves a 1,5-*anti* aldol between **5** and the product of **3** and **4**, in which C11 would exist in the aldehyde oxidation state. The synthesis of an analog of (–)-**5** (without the Et group) and 1,5-aldol studies have previously been reported by us,[18] in which we demonstrated that a >99:1 selectivity and 94% yield could be achieved in this coupling. The synthesis of this analog was

[a] Department of Chemistry, University of Wyoming, Laramie, Wyoming 82071-3838, USA
Fax: +1-307-766-2807
E-mail: hoberg@uwyo.edu
[b] School of Chemical and Physical Sciences, Victoria University of Wellington, Wellington, New Zealand
[c] Malaghan Institute of Medical Research, Wellington, New Zealand

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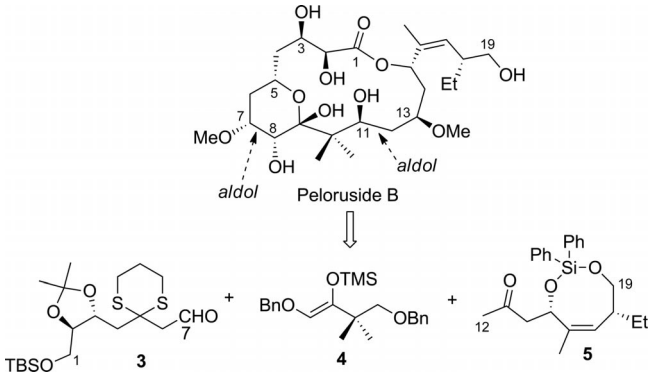
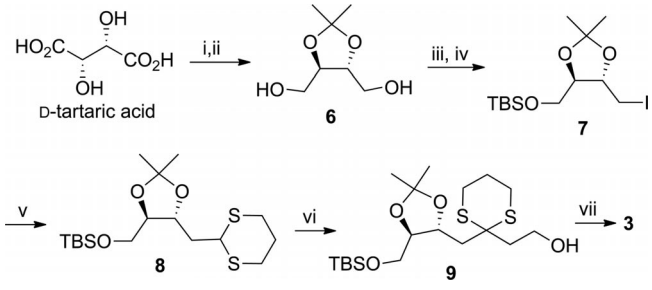
achieved in four steps in 33% overall yield. Following our approach, Casey et al. have since synthesized the required (+)-**5** as a single diastereoisomer.[19]



Scheme 1. Retrosynthetic strategy for the synthesis of peloruside B.

Results and Discussion

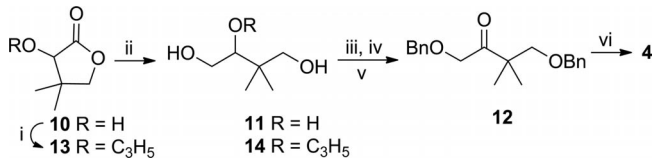
The synthesis of aldehyde **3** commenced with D-tartaric acid to set the absolute configuration (Scheme 2). A one-step protection gave the 2,3-acetonide dimethyl ester,[20,21] which was then reduced[22] to provide diol **6**. Mono protection of one alcohol with *t*BuMe$_2$SiCl[23] followed by iodination[24] of the remaining hydroxy group gave **7** in an excellent 67% overall yield over the four steps. Treatment of iodo **7** with the lithium anion of 1,3-dithiane produced dithiane **8**,[24] which was then further lithiated and treated with ethylene oxide formed in situ from 2-bromoethanol to form alcohol **9**. Finally, Swern oxidation of **9** provided aldehyde **3** in an overall yield of 24% over seven steps. This strategy represents rapid access to the C1–C7 fragment.



Scheme 2. Reagents and conditions: (i) $(MeO)_2CMe_2$, *p*TsOH, MeOH, r.t., 84%; (ii) $LiAlH_4$, Et_2O, reflux, 99%; (iii) NaH then TBSCl, THF, 93%; (iv) I_2, Ph_3P, imidazole, PhMe, 60 °C, 87%; (v) 1,3-dithiane, *t*BuLi, THF/HMPA, 69%; (vi) 2-bromoethanol, *t*BuLi, THF/HMPA, 83%; (vii) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, 76%.

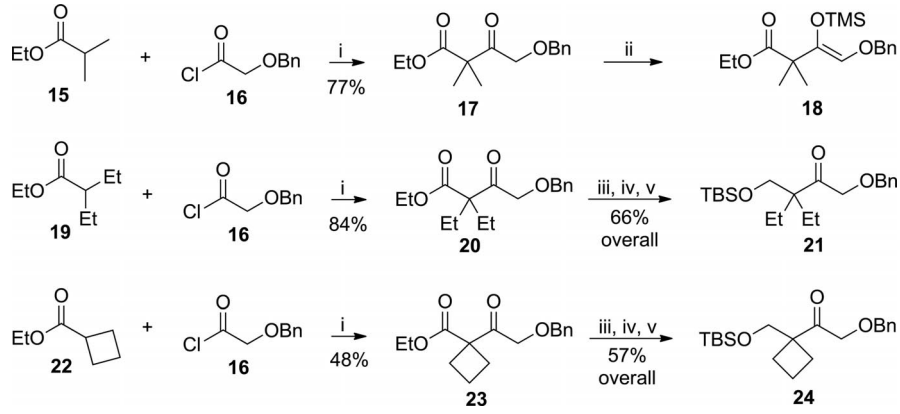
Synthesis of fragment **4** was based on two alternative strategies. The first began with the use of commercially available pantolactone (**10**, Scheme 3), while the second involved an initial Claisen-type reaction (Scheme 4). This latter strategy has the advantage of being amenable to the introduction of alternative groups at the C10 position.

To this end, the synthesis of enol ether **4** commenced with commercially available pantolactone **7**, which upon reduction is reported to provide *gem*-dimethyl triol **11** (Scheme 3). A planned benzylation of the primary alcohols followed by oxidation of the remaining secondary alcohol would potentially provide **12** in three straightforward steps. Thus, pantolactone was reduced with $LiAlH_4$ to triol **11** according to literature procedures.[25] However, it was found that this approach gave poor yields and very problematic purification; therefore, the strategy was modified to first include the protection of **10** as an allyl ether. Using one equivalent of KO*t*Bu, allyl ether **13** was prepared in good yield. Several other protecting groups, such as silyl ethers and methoxymethyl ether, were also used; however, these displayed poor stability in subsequent reactions. Reduction of lactone **13** with $LiAlH_4$ gave diol **14** in 76% yield and was highly reproducible. Benzyl protection of the resulting primary alcohols under standard conditions followed by palladium-catalyzed deprotection and oxidation gave *gem*-dimethyl butanone **12**. Final silyl enol formation proved to be very facile and gave silyl enol ether **4** as a highly stable, single isomer in an overall 44% yield over the six steps. The (*Z*) stereochemistry of **4** was established by NOE experiments, in which positive correlations were observed between the vinylic proton and the *gem*-dimethyl groups. This stereochemistry is perhaps due to chelation of the enolate lithium ion and the benzyl oxygen during enol ether formation.

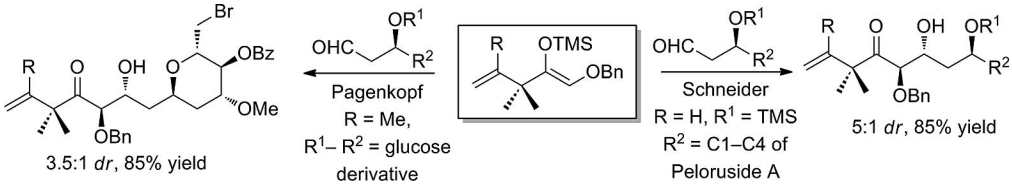


Scheme 3. Reagents and conditions: (i) KO*t*Bu (1.1 equiv.) then C_3H_5Br, DMF, 88%; (ii) $LiAlH_4$, THF, reflux, 76%; (iii) NaH then BnBr, THF, 93%; (iv) $TolSO_2H$, $Pd(Ph_3P)_4$, THF, 84%; (v) PCC, NaOAc, 89%; (vi) LDA then TMSCl, 95%.

In an attempt to develop a shorter synthesis of **4**, the alternative Claisen-type strategy depicted in Scheme 4 was pursued. This strategy involved an LDA-mediated coupling of ethyl isobutanoate (**15**) with benzyloxyacetyl chloride (**16**), which is formed in a one-pot reaction according to a literature procedure.[26] Desired ester **17** was obtained in good yield; however, formation of enol silane **18** produced multiple products, two of which were the (*E*) and (*Z*) isomers. Purification of the mixture proved to be futile and efforts at obtaining this analog of **4** were abandoned. While this route did not provide a shorter route to **4**, it did provide access to analogs of **4**. Development of analogs at this position was deemed important, as binding studies have indicated that this peloruside moiety plays an important role in binding to the active site.[17,27] Thus, Claisen reaction of **16** with appropriate ester **19** or **22** gave β-keto esters **20** and **23**, respectively, in very good to moderate yields. These β-keto esters were then transformed into analogs of **12** using the methods previously established above. The enolsilane of **21** has also been synthesized in 87% yield to give the *gem*-diethyl analog of **4** with modified protecting groups, but has not been treated with **3** to date.



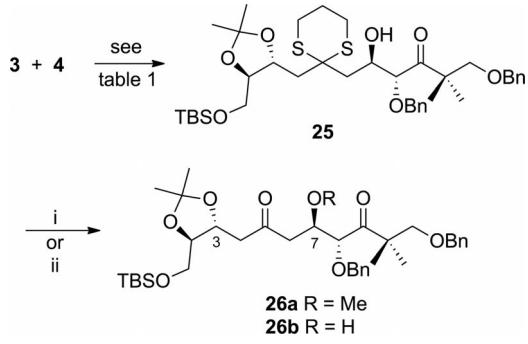
Scheme 4. Reagents and conditions: (i) LDA, THF then **16**; (ii) LDA, then TMSCl; (iii) $LiAlH_4$, THF, reflux, 2 h; (iv) TBSCl, imidazole, DMF, r.t., 12 h; (v) PCC, NaOAc, r.t., 5 h.



Scheme 5. Aldol reactions of analogs of **4** reported by Pagenkopf and Schneider.

With the C1–C7 (**3**) and C8–C11 (**4**) fragments of peloruside in hand, and methodology that enables analogs of **1** to be prepared, the critical Mukiayama aldol reaction between **3** and **4** was ready. Both the Pagenkopf[28] and Schneider[29] groups have reported aldol reactions as illustrated in Scheme 5. This silyl enol ether analog (boxed structure) of enol ether **4** provides the desired *anti*,*anti* diastereomer in both cases and produces excellent yields. Furthermore, Mukiayama aldol reactions involving 1,5-asymmetric induction to produce high *anti*,*anti* diastereomeric ratios, as required in our reaction, have been reported using remote sulfinyl groups.[30] These 1,5-asymmetric reactions have been extended to reductions[31] and hydrocyanations.[32] Finally, an abundance of 1,5 *anti*-aldol reactions using β-oxygenated boron enolates have been reported,[33] in which a boat-like transition state has been implicated.[34] Thus, excellent precedence existed for the formation of an *anti*,*anti* diastereomer in the Mukiayama aldol reaction of our enol ether **4** with aldehyde **3**.

The results of our aldol reaction are as indicated in Scheme 6 and Table 1. A variety of conditions were attempted, and it soon became apparent that the type and number of equivalents of Lewis acid greatly influenced the reaction outcome, as did the equivalents of aldehyde **1**. Comparison of Entries 1–3 (Table 1) illustrate this point in which deviation from the optimized conditions in Entry 3 (Table 1) drastically affected the ratio of recovered ketone **12** and desired product **25**. With less than one equivalent of acid (Table 1, Entry 1), adduct **25** was obtained in a poor 16% yield. Subsequently, the amount of $TiCl_4$ was increased and produced a promising increase in the amount of **25**, along with small amounts of an isomer (Table 1, Entry 2). Given this, we then increased the number of equivalents of Lewis acid and aldehyde **1** and, to our delight, observed aldol adduct **25** as a single isomer in 76% yield, with complete consumption of enol ether **2** (Table 1, Entry 3). Finally, we tested several additional Lewis acids (Table 1, Entries 4–6), but poor results were obtained. The use of boron Lewis acids (Table 1, Entries 4 and 5) gave poor yields of **25**, and $SnCl_4$ (Table 1, Entry 6) produced none of desired aldol adduct **25**. Aldol product **25** represents the C1–C11 carbon framework of peloruside, in which only deprotection of the dithiane remained.



Scheme 6. Reagents and conditions: (i) R = Me: Me_3OBF_4 (15 equiv.), proton sponge (15 equiv.), CH_2Cl_2, r.t., 11%; (ii) R = H: MeI, $CaCO_3$, MeCN/H_2O, reflux 18 h, 87%.

Our initial attempt at removal of the dithiane involved concurrent methylation of the C7 hydroxy and deprotection to give **26a** (Scheme 6, conditions i). This accomplished the desired transformation; however, the yield was disappointing at 11%. Despite multiple modifications to the pro-

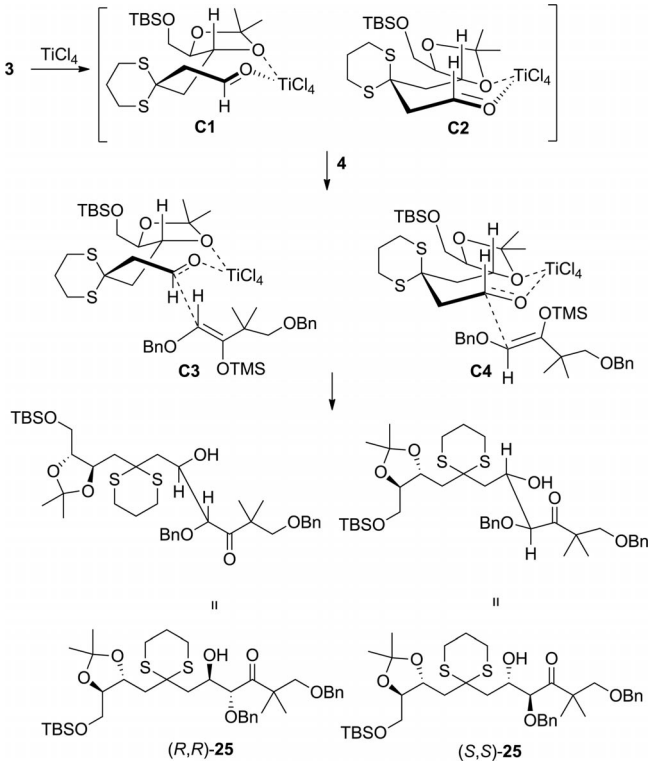
Table 1. Aldol reaction between **3** and **4**.[a,b]

Entry	Lewis Acid (equiv.)	**3** [equiv.]	**4** [equiv.]	Yield [%] **12**	**25**
1	$TiCl_4$ (0.5)	1	1	71	16
2	$TiCl_4$ (1)	1	1	45	32
3	$TiCl_4$ (2)	2	1	0	76
4	BF_3OEt_2 (1)	1	1	35	6
5	(–)-$(Ipc)_2BOTf$ (1)	1	1	24	25
6	$SnCl_4$ (1)	1	1	0	0

[a] Yields determined on purified material. [b] Ratios of products determined on crude material.

cedure, this yield could not be improved. Thus, we focused on the deprotection of the dithiane, initially using standard mercury protocol ($HgO/HgCl_2$). Although this gave desired product **26b**, a disappointing yield of 44% was obtained. Nonetheless, a successful deprotection was achieved in an excellent yield of 87% using MeI and $CaCO_3$, providing us with the core C1–C11 fragment of peloruside B.

In addition to providing rapid entry into the C1–C11 framework of peloruside B, perhaps the most remarkable aspect about this strategy is the selectivity observed in the coupling of **3** and **4**, particularly given the remoteness of the nearest stereogenic center. This 1,5-*anti* stereoselectivity between C3 and C7 can be rationalized based on work reported by Reetz and co-workers,[35] where they observed that $TiCl_4$ activates the aldehyde for enolsilane attack by forming a chelate with the aldehyde oxygen atom and an α- or β-alkoxy substituent. In this instance, we propose chelation of the titanium with both the C3 oxygen of the acetonide and the aldehyde oxygen at C7 (Scheme 7). Conformations **C1** and **C2** lead to attack at either the *Si* or *Re* face, respectively, and are approached by the enolsilane via an acyclic transition state, in which the silyl group does not interact with the oxygen of the aldehyde carbonyl.[35–37] Approach of the enolsilane as in both **C3** and **C4** represents the least sterically hindered transition states and produces either the (*R*,*R*) or (*S*,*S*) isomers. In order to establish the stereochemistry of **25**, Mosher's method was applied using 2-methoxy-2-phenyl-2-(trifluoromethyl)acetic acid,[38] and the existence of **25** in the (*R*,*R*) state was indicated. To authenticate the stereochemistry, attempts at growing crystals of **26** or derivatives of it were attempted for X-ray crystallography; however, we were unsuccessful in obtaining crystals and thus additional confirmation of the proposed stereochemistry has not been obtained.



Scheme 7. Proposed conformations and transition states leading to (*R*,*R*)-**25** and (*S*,*S*)-**25**.

Conclusion

We have successfully constructed the C1–C11 fragment of peloruside B in a total of 15 steps by using D-tartaric acid to set the absolute stereochemistry. Gratifying, the key aldol reaction occurs with remarkable stereochemistry through a 1,5-*anti*,*anti* Mukiayama aldol reaction. The methodology allows the framework of the pelorusides to be synthesized in a remarkably efficient manner and enables changes to be made at the C10 position.

Experimental Section

General Procedures: All reagents were of commercial quality, and solvents were dried prior to use via standard procedures. Standard syringe techniques were used for all reactions, and all reactions were carried out under an atmosphere of argon unless otherwise noted. Reaction progress was monitored by using precoated TLC plates with silica UV254 and visualized by either UV radiation (254 nm) or ceric ammonium molybdate dip. Flash chromatography was performed using silica gel 60 (220–240 mesh) with the solvent systems as indicated. ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance 400, a Varian 300, or a Varian 500 NMR spectrometer and referenced to solvent peaks (^1H, residual $CHCl_3$; ^{13}C, $CDCl_3$). Accurate masses were recorded on Mariner time-of-flight spectrometers. Compounds **6**,[20–22] **7**,[23,24] and **8**[24] were synthesized as described previously and spectroscopic data matched that of previously published spectra.[39]

3-Allyloxy-dihydro-4,4-dimethyl-2(3*H*)-furanone (13): To a solution of pantolactone (10.0 g, 76.8 mmol) in DMF (80 mL) at 0 °C was added a solution of potassium *tert*-butoxide (1 M in THF, 76.8 mL, 76.8 mmol). The cooling bath was then removed, and the solution was stirred at room temperature for 30 min. A solution of allyl bromide (6.99 mL, 80.6 mmol) in THF (7 mL) was then added dropwise, and the resulting mixture stirred at room temperature overnight before being quenched with water and extracted with Et_2O (2×). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (2×) and brine (1×), dried with $MgSO_4$, and concentrated under reduced pressure. Flash chromatography of the crude product (hexanes/EtOAc, 5:1) gave **13** (10.6 g, 81%) as a colorless oil. ^1H NMR: δ = 5.90 (m, 1 H, 2′-H), 5.32 (dd, J = 17.1, 1.2 Hz, 1 H, 3a′-H), 5.24 (d, J = 10.2 Hz, 1 H, 3b′-H), 4.46 (dd, J = 12.9,

5.1 Hz, 1 H, 1′-H), 4.20 (dd, *J* = 12.9, 6.3 Hz, 1 H, H1b′), 3.99 (d, *J* = 8.7 Hz, 1 H, 5a-H), 3.89 (d, *J* = 8.7 Hz, 1 H, 5b-H), 3.74 (s, 1 H, 3-H), 1.17 (s, 3 H, Me), 1.10 (s, 3 H, Me) ppm. ^{13}C NMR: δ = 175.3 (C2), 133.8 (C2′), 118.0 (C3′), 80.7 (C1′), 76.3 (C3), 71.6 (C5), 40.3 (C2), 23.3 (Me), 19.2 (Me) ppm. IR (neat): $\tilde{\nu}$ = 2971, 1788, 1124 cm^{-1}. HRMS: calcd for $C_9H_{14}O_3$ [M + H]$^+$ 171.1016; found 171.1020.

3-Allyloxy-2,2-dimethyl-butane-1,4-diol (14): A 25 mL flask equipped with side arm and reflux condenser was charged with $LiAlH_4$ (305 mg, 7.85 mmol) and THF (10 mL). A solution of **13** (891 mg, 5.23 mmol) in THF (5 mL) was then added cautiously dropwise over 15 min. The resulting solution was heated at reflux for 3 h before being cooled to 0 °C and quenched by the portionwise addition of hydrated sodium sulfate. The residue was diluted with ethanol (50 mL), filtered though a 0.5 cm × 3 cm diameter silica gel plug, dried with anhydrous Na_2SO_4, and the solvents were removed under reduced pressure. Flash chromatography of the crude product (hexanes/EtOAc, 1:1) gave **14** (690 mg, 76%) as a colorless oil. ^{1}H NMR: δ = 5.95 (m, 1 H, 2′-H), 5.29 (dd, *J* = 17.1, 1.5 Hz, 1 H, 3a′-H), 5.19 (dd, *J* = 10.5, 1.2 Hz, 1 H, 3b′-H), 4.19 (ddt, *J* = 12.6, 5.4, 1.5 Hz, 1 H, 1a′-H), 4.07 (ddt, *J* = 12.6, 5.4, 1.5 Hz, 1 H, 1b′-H), 3.80 (dd, *J* = 12.0, 3.90 Hz, 1 H, 4a-H), 3.70 (dd, *J* = 12.0, 4.2 Hz, 1 H, 4b-H), 3.51 (d, *J* = 11.2 Hz, 1 H, 1a-H), 3.35 (d, *J* = 11.2 Hz, 1 H, 1b-H), 3.20 (dd, *J* = 4.2, 3.9 Hz, 1 H, 3-H), 2.36 (br. s, 2 H, O*H*), 0.96 (s, 3 H, Me), 0.94 (s, 3 H, Me) ppm. ^{13}C NMR: δ = 134.7 (C2′), 117.1 (C3′), 85.7 (C1′), 72.6 (C3), 69.1, (C1) 60.6 (C4), 39.1 (C2), 23.0 (Me), 21.3 (Me) ppm. IR (neat): $\tilde{\nu}$ = 3345, 2967, 2876, 1048 cm^{-1}. HRMS: calcd for $C_9H_{18}O_3$ [M + H]$^+$ 175.1334; found 175.1329.

3-Allyloxy-1,4-bis(benzyloxy)-2,2-dimethyl-butane (14a): To a 25 mL flask containing NaH (491 mg, 20.5 mmol, washed 3× with hexanes) in DMF (6.5 mL) at 0 °C was added a solution of **14** (713 mg, 4.09 mmol) in DMF (5 mL) over 5 min. When gas evolution had ceased, benzyl bromide (998 μL, 8.39 mmol) was added dropwise, and the reaction mixture was warmed to room temperature overnight. The solution was then cautiously quenched with water and extracted with Et_2O (2×), and the combined organic extracts were washed with sat. aq. $NaCO_3$ solution (2×) and brine (1×), dried with $MgSO_4$, and concentrated under reduced pressure. Flash chromatography of the crude product (hexanes) gave **14a** (1.30 g, 90%) as a colorless oil. ^{1}H NMR: δ = 7.32 (m, 10 H, Ph-H), 5.93 (m, 1 H, 2′-H), 5.24 (dd, *J* = 17.1, 1.8 Hz, 1 H, 3a′-H), 5.10 (dd, *J* = 10.2, 1.5 Hz, 1 H, 3b′-H), 4.52 (s, 2 H, CH_2Ph), 4.46 (s, 2 H, CH_2Ph), 4.34 (ddt, *J* = 12.6, 5.4, 1.5 Hz, 1 H, 1a′-H), 4.03 (ddt, *J* = 12.6, 5.4, 1.5 Hz, 1 H, 1b′-H), 3.71 (m, 1 H, 4a-H), 3.58 (m, 2 H, 3-H, 4b-H), 3.38 (d, *J* = 8.7 Hz, 1 H, 1b-H), 3.15 (d, *J* = 8.7 Hz, 1 H, 1b-H), 0.95 (s, 3 H, Me) 0.92, (s, 3 H, Me) ppm. ^{13}C NMR: δ = 138.9 (Ph), 138.6 (Ph), 135.8 (C2′), 128.3 (Ph), 127.8 (Ph), 127.7 (Ph), 127.4 (Ph), 115.7 (C3′), 82.5 (C1′), 77.2 (*C*H_2Ph), 77.1 (*C*H_2Ph), 74.5, 73.2, 72.0 (C1, C3, C4), 38.7 (C2), 20.9 (Me), 22.2 (Me) ppm. IR (neat): $\tilde{\nu}$ = 3028, 2906, 2859, 1092 cm^{-1}.

1,4-Dibenzyloxy-3,3-dimethylbutan-2-ol (14b): *p*-Toluenesulfinic acid (82 mg, 0.52 mmol) was added at room temperature to a solution of **14a** (167 mg, 0.47 mmol) and $Pd(PPh_3)_4$ (33 mg, 0.03 mmol) in THF (4.7 mL). The reaction mixture was stirred at room temperature for 7 h before Et_3N (13 μL) was added. The solvent was then removed under reduced pressure, and the residue was purified immediately by gradient flash chromatography (hexanes/EtOAc, 50:1 to 20:1) to give **14b** (122 mg, 83%) as a colorless oil. ^{1}H NMR: δ = 7.37 (m, 10 H, Ph), 4.57 (s, 2 H, CH_2Ph), 4.50 (s, 2 H, CH_2Ph), 3.78 (ddd, *J* = 8.4, 3.3, 3.0 Hz, 1 H, 3-H), 3.64 (dd, *J* = 9.6, 3.0 Hz, 1 H, 4a-H), 3.49 (dd, *J* = 9.6, 8.4 Hz, 1 H, 4b-H), 3.38 (d, *J* = 8.7 Hz, 1 H, 1a-H), 3.27 (d, *J* = 8.7 Hz, 1 H, 1b-H), 3.03 (d, *J* = 3.3 Hz, 1 H, O*H*), 0.97 (s, 3 H, Me), 0.96 (s, 3 H, Me) ppm. ^{13}C NMR: δ = 138.4 (Ph), 129.5 (Ph), 128.2 (Ph), 127.8 (Ph), 127.6 (Ph), 127.5 (Ph), 78.2 (*C*H_2Ph), 75.7 (*C*H_2Ph), 73.4, 73.3, 71.7 (C1, C3, C4), 37.4 (C2), 21.6 (Me), 20.3 (Me) ppm. IR (neat): $\tilde{\nu}$ = 3498, 2987, 2848, 1105 cm^{-1}. HRMS: calcd. for $C_{20}H_{26}O_3$ 315.1950 [M + H]$^+$; found 315.1955.

1,4-Dibenzyloxy-3,3-dimethyl-2-butanone (12): To a solution of **14b** (100 mg, 0.32 mmol) in CH_2Cl_2 (1.6 mL) was added pyridinium dichromate (181 mg, 0.48 mmol), freshly activated 3 Å molecular sieves powder (260 mg) then anhydrous AcOH (32 μL, 0.55 mmol). The reaction was stirred at room temperature for 15 min before being diluted with CH_2Cl_2 and filtered though a small (0.5 cm) bilayer Celite/silica gel plug. The filtrate was washed with water then brine, and the organic phase was dried with $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (hexanes/EtOAc, 50:1) to give **12** (81 mg, 82%) as a colorless oil. ^{1}H NMR: δ = 7.35 (m, 10 H, Ph-H), 4.58 (s, 2 H, CH_2Ph), 4.48 (s, 2 H, CH_2Ph), 4.38 (s, 2 H, 1-H), 3.44 (s, 2 H, 4-H), 1.17 (s, 6 H, 2 Me) ppm. ^{13}C NMR: δ = 210.8 (C3), 138.2 (Ph), 137.8 (Ph), 128.7 (Ph), 128.6 (Ph), 128.2 (Ph), 128.1 (Ph), 127.9 (Ph), 127.8 (Ph), 77.3 (*C*H_2Ph), 73.6 (*C*H_2Ph), 73.3, 72.4 (C1, C4), 47.6 (C2), 22.1 (2 Me) ppm. IR (neat): $\tilde{\nu}$ = 3031, 2967, 2932, 2869, 1723, 1100 cm^{-1}. HRMS: calcd. for $C_{20}H_{24}O_3$ 313.1805 [M + H]$^+$; found 313.1798.

(*Z*)-1,4-Dibenzyloxy-3,3-dimethyl-2-(trimethylsilyloxy)-1-butene (4): A stirred solution of diisopropylamine (0.390 mL, 2.79 mmol) in THF (5 mL) was cooled to 0 °C and *n*BuLi (1.6 M in hexane, 1.74 mL, 2.79 mmol) then added. The mixture was stirred at 0 °C for 20 min and then cooled to –78 °C, at which temperature **12** (580 mg, 1.86 mmol) was added as a solution in THF (5 mL). Stirring was continued at –78 °C for 30 min during which time the solution developed a bright yellow color. TMSCl (0.375 mL, 321 mg, 2.79 mmol) was added, and the mixture was stirred at –78 °C for 30 min and then warmed to room temperature for 1 h. The reaction was quenched by the addition of water (2 mL) and extracted with hexanes (3 × 10 mL). The combined organic fractions were washed with water (5 mL) and brine (10 mL) and dried with $MgSO_4$, and the solvents were removed under reduced pressure. Only the (Z)-isomer was detectable in the ^{1}H NMR spectrum of the crude product, as determined by NOE experiments. Purification by flash column chromatography (hexanes/EtOAc, 50:1; neutralized with a few drops of Et_3N) gave **4** (680 mg, 95%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ = 7.35–7.25 (m, 10 H, Ph-H), 5.67 (s, 1 H, 1-H), 4.70 (s, 2 H, CH_2Ph), 4.51 (s, 2 H, CH_2Ph), 3.26 (s, 2 H, 4-H), 1.02 (s, 6 H, 2 Me), 0.12 [s, 9 H, Si(CH_3)$_3$] ppm. ^{13}C NMR ($CDCl_3$): δ = 140.5 (C-2), 139.0 (Ph), 137.5 (Ph), 128.3 (Ph), 128.2 (Ph), 127.9 (Ph), 127.7 (Ph), 127.4 (Ph), 127.2 (C-2), 76.7 (C-4), 73.7 (CH_2Ph), 73.1 (CH_2Ph), 38.8 (C-3), 23.0 (2 Me), 0.7 [Si(CH_3)$_3$] ppm. IR (neat): $\tilde{\nu}$ = 2958, 2863, 1679, 1496, 1247, 1205, 1098, 1027, 843, 731 cm^{-1}. HRMS: calcd. for $C_{23}H_{32}O_3Si$ 385.2199 [M + H]$^+$; found 385.2187.

Ethyl 4-(Benzyloxy)-2,2-dimethyl-3-oxobutanoate (17): A stirred solution of diisopropylamine (0.421 mL, 3.00 mmol) in THF (5 mL) was cooled to 0 °C and *n*BuLi (1.4 M in hexane, 2.1 mL, 3.00 mmol) was then added. The mixture was stirred at 0 °C for 20 min and then cooled to –78 °C, at which temperature ethyl isobutyrate (**15**; 0.402 mL, 3.00 mmol) was added as a solution in THF (2 mL). The mixture was stirred for 20 min at –78 °C and then 20 min at 0 °C. The mixture was cooled to –78 °C and 2-(benzyloxy)acetyl chloride (**16**; 609 mg, 3.30 mmol) was added dropwise. After stirring for 40 min, the mixture was quenched with water,

extracted with CH_2Cl_2 (3×), and dried with $MgSO_4$. Flash chromatography (EtOAc/cyclohexane, 1:10) gave **17** (580 mg, 73%) as a colorless oil. ^1H NMR ($CDCl_3$): δ = 7.24 (m, 5 H, Ph-H), 4.46 (s, 2 H, CH_2Ph), 4.12 (s, 2 H, 4-H), 4.00 (q, J = 7.4 Hz, 2 H, OCH_2Me), 1.29 (s, 6 H, 2 Me), 1.09 (t, J = 7.4 Hz, 3 H, OCH$_2$*Me*) ppm. ^{13}C NMR ($CDCl_3$): δ = 205.5 (C-3), 172.9 (C-1), 136.9 (Ph), 128.3 (Ph), 127.9 (Ph), 127.5 (Ph), 73.1 (-O*C*H$_2$Ph), 72.7 (*C*-4), 61.0 (O*C*H$_2$Me), 53.2 (C-2), 21.6 (2 Me), 13.8 (OCH$_2$*Me*) ppm. IR (neat): $\tilde{\nu}$ = 2930, 2339, 1786, 1722, 1505, 1275 cm^{-1}.

2-(2-{[(4*R*,5*R*)-5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-1,3-dithian-2-yl)ethanol (9): To a solution of 2-bromoethanol (84 μL, 1.19 mmol) in THF/HMPA (10:1, 3.3 mL) at –15 °C was added *t*BuLi (700 μL, 1.19 mmol), and the reaction mixture was stirred for 1 h at –15 °C. In a separate flask, dithiane **8** (300 mg, 0.79 mmol) in THF/HMPA (10:1, 2.2 mL) was cooled to –78 °C and *t*BuLi (465 μL, 0.79 mmol) was added to the solution, and then stirred for 30 min at –78 °C. The initial mixture was cannulated into the dithiane mixture at –78 °C, stirred for 2 h at –78 °C, and then slowly warmed to room temperature. The reaction was quenched by the addition of sat. NH_4Cl. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×). The organic phases were combined, washed with sat. $NaHCO_3$ and brine, and dried with anhydrous Na_2SO_4. After filtration and concentration, the resulting oil was purified by flash chromatography (EtOAc/cyclohexane, 1:3) to give **9** (280 mg, 83%) as a colorless oil. ^1H NMR ($CDCl_3$): δ = 4.30 (ddd, J = 9.3, 8.3, 1.3 Hz, 1 H, 5-H), 3.95–3.85 (m, 2 H, 1-H), 3.84 (dd, J = 10.6, 3.8 Hz, 1 H, 7-H), 3.75 (dd, J = 10.6, 5.5 Hz, 1 H, 7-H), 3.70 (ddd, J = 8.3, 5.5, 3.8 Hz, 1 H, 6-H), 2.83–2.68 (m, 4 H, S-CH$_2$-CH$_2$-CH$_2$-S), 2.49 (d, J = 15.4 Hz, 1 H, 2-H), 2.41–2.23 (m, 3 H, 2-H, 6), 2.00–1.95 (m, 2 H, S-CH$_2$-CH$_2$-CH$_2$-S), 1.41 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 0.92 [s, 9 H, SiC(CH_3)$_3$], 0.10 [s, 6 H, Si(CH_3)$_2$] ppm. ^{13}C NMR ($CDCl_3$): δ = 109.1, 80.8, 75.7, 63.2, 59.1, 51.3, 41.6, 40.8, 27.1, 26.9, 26.8, 26.1, 25.9, 25.8, 25.0, 18.3, –5.4, –5.5 ppm. IR (neat): $\tilde{\nu}$ = 3450, 2950, 2920, 2850, 1470, 1380, 1250, 1090, 840, 780 cm^{-1}. MS: calcd. for $C_{19}H_{38}O_4S_2Si$ [M + H] 423.2060; found 423.2054.

2-(2-{[(4*R*,5*R*)-5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-1,3-dithian-2-yl)acetaldehyde (3): To a solution of oxalyl chloride (60 μL, 0.71 mmol) in CH_2Cl_2 (3 mL) was added DMSO (102 μL, 1.42 mmol) at –78 °C. After 5 min, a solution of alcohol **9** (150 mg, 0.35 mmol) in CH_2Cl_2 (3 mL) was added, and the reaction mixture was stirred at –78 °C for 15 min. Triethylamine was added, and the mixture was stirred for an additional 15 min, then the reaction mixture was concentrated, dissolved in EtOAc/cyclohexane (1:10), filtered, and concentrated. Flash chromatography (EtOAc/cyclohexane, 1:10) gave **3** (141 mg, 76%) as a pale yellow oil. ^1H NMR ($CDCl_3$): δ = 9.82 (dd, J = 2.3, 2.3 Hz, 1 H, 1-H), 4.30 (ddd, J = 9.8, 7.8, 1.3 Hz, 1 H, 5-H), 3.86 (ddd, J = 13.3, 3.5, 3.3 Hz, 1 H, 7-H), 3.76–3.67 (m, 2 H, 7-H, 6-H), 3.01 (dd, J = 17.1, 2.8 Hz, 1 H, 2-H), 2.98 (dd, J = 17.1, 2.3 Hz, 1 H, 2-H), 2.93–2.75 (m, 4 H, S-CH$_2$-CH$_2$-CH$_2$-S), 2.61 (d, J = 15.1 Hz, 1 H, 4-H), 2.21 (d, J = 15.1, 9.8 Hz, 1 H, 4-H), 2.03–1.93 (m, 2 H, S-CH$_2$-CH$_2$-CH$_2$-S), 1.37 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 0.92 [s, 9 H, SiC(CH_3)$_3$], 0.10 [s, 6 H, Si(CH_3)$_2$] ppm. ^{13}C NMR ($CDCl_3$): δ = 207.7, 109.1, 80.8, 75.7, 63.2, 59.1, 51.3, 41.6, 40.8, 27.1, 26.9, 26.1, 25.9, 25.0, 18.3, –5.4, –5.5 ppm. IR (neat): $\tilde{\nu}$ = 2920, 1720, 1250, 1090, 840 cm^{-1}. MS: calcd. for $C_{19}H_{36}O_4S_2Si$ [M + H] 421.1901; found 421.1900.

(4*R*,5*R*,9*R*,10*R*)-1,4-Bis(benzyloxy)-11-(*tert*-butyldimethylsilyloxy)-9,10-(2,2-dimethyl-1,3-dioxolane)-7-(1,3-dithiane)-5-hydroxy-2,2-dimethylundecan-3-one (25): $TiCl_4$ (164 μL, 1.50 mmol) was added to a–78 °C solution of aldehyde **3** (630 mg, 1.50 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 15 min before enol silane **4** (288 mg, 0.75 mmol) was added at the same temperature. The solution was warmed to –20 °C slowly and stirred overnight at that temperature. The reaction was quenched by the addition of sat. NH_4Cl. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×). The organic phases were combined, washed with brine, and dried with anhydrous Na_2SO_4. After filtration and concentration, the resulting oil was purified by flash chromatography (EtOAc/cyclohexane, 1:10) to yield **25** (418 mg, 76%) as a single isomer. ^1H NMR ($CDCl_3$): δ = (4-H and 6-H not rigorously assigned): δ = 7.33–7.26 (m, 10 H, Ph), 4.54 (d, J = 11.3 Hz, 1 H, CH_2Ph), 4.48 (s, 2 H, CH_2Ph), 4.44 (d, J = 5.3 Hz, 1 H, 4-H), 4.46–4.36 (m, 1 H, 5-H), 4.41 (d, J = 11.3 Hz, 1 H, CH_2Ph), 4.31–4.25 (m, 1 H, 9-H), 3.79 (dd, J = 10.8, 4.3 Hz, 1 H, 11-H), 3.72 (dd, J = 10.8, 5.3 Hz, 1 H, 11-H), 3.65 (ddd, J = 8,3, 5.0, 4.3 Hz, 1 H, 10-H), 3.57 (d, J = 8.8 Hz, 1 H, 1-H), 3.51 (d, J = 8.8 Hz, 1 H, 1-H), 3.35 (d, J = 5.3 Hz, 1 H, 5-H), 2.92–2.64 (m, 4 H, S-CH$_2$-CH$_2$-CH$_2$-S), 2.42 (dd, J = 15.6, 8.3 Hz, 1 H, 6-H), 2.41 (dd, J = 15.4, 8.1 Hz, 1 H, 4-H), 2.28 (dd, J = 15.6, 8.6 Hz, 1 H, 6-H), 2.14 (dd, J = 15.4, 8.8 Hz, 1 H, 4-H), 1.96–1.86 (m, 2 H, S-CH$_2$-CH$_2$-CH$_2$-S), 1.38 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 0.90 [s, 9 H, SiC(CH_3)$_3$], 0.08 (s, 3 H, SiCH_3), 0.07 (s, 3 H, SiCH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 214.1, 137.8, 137.8, 128.2, 128.1, 127.6, 127.5, 127.5, 127.5, 109.0, 83.1, 81.0, 77.7, 75.4, 73.3, 71.7, 69.4, 63.2, 51.6, 48.5, 43.2, 41.2, 27.2, 26.9, 26.8, 26.3, 25.9, 25.8, 24.6, 22.1, 22.0, 18.3, –5.4, –5.4 ppm. IR (neat): $\tilde{\nu}$ = 3440, 2930, 2850, 1710, 1460, 1370, 1250, 1090, 840, 780, 740, 690 cm^{-1}. MS: calcd. for $C_{39}H_{60}O_7S_2Si$ [M + H] 733.3629; found 733.3618.

(4*R*,5*R*,9*R*,10*R*)-1,4-Bis(benzyloxy)-11-(*tert*-butyldimethylsilyloxy)-9,10-(2,2-dimethyl-1,3-dioxolane)-5-methoxy-2,2-dimethylundecan-3,7-dione (26a): A solution of **25** (20 mg, 0.027 mmol) in CH_2Cl_2 was added to a mixture of Me_3OBF_4 (32 mg, 0.22 mmol) and 1,8-bis(dimethylaminonaphthalene) (Proton Sponge, 47 mg, 0.22 mmol) in CH_2Cl_2 at room temperature. The mixture was stirred for 2 h, and then the solvent was removed under reduced pressure. Flash chromatography (EtOAc/cyclohexane, 1:10) gave **26a** (2 mg, 11%) as a colorless oil. ^1H NMR ($CDCl_3$): δ = 7.33–7.22 (m, 10 H, Ph-H), 4.57 (d, J = 14.8 Hz, 1 H, CH_2Ph), 4.53 (d, J = 4.0 Hz, 1 H, C-4), 4.49 (d, J = 11.8 Hz, 2 H, CH_2Ph), 4.28 (ddd, J = 7.8, 7.6, 4.0 Hz, 1 H, 9-H), 4.23 (d, J = 14.8 Hz, 1 H, CH_2Ph), 4.21 (ddd, J = 6.8, 5.5, 4.0 Hz, 1 H, 5-H), 3.80 (dd, J = 13.1, 7.1 Hz, 1 H, 11-H), 3.67 (dd, J = 13.1, 5.8 Hz, 1 H, 11-H), 3.66 (ddd, J = 7.6, 7.1, 5.8 Hz, 1 H, 10-H), 3.60 (d, J = 8.8 Hz, 1 H, 1-H), 3.48 (d, J = 8.8 Hz, 1 H, 1-H), 3.27 (s, 3 H, OCH_3), 2.86 (dd, J = 17.6, 5.5 Hz, 1 H, 6-H), 2.69 (dd, J = 17.6, 6.8 Hz, 1 H, 6-H), 2.66 (dd, J = 16.4, 4.0 Hz, 1 H, 4-H), 2.61 (dd, J = 16.4, 7.8 Hz, 1 H, 4-H), 1.37 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 0.89 [s, 9 H, SiC(CH_3)$_3$], 0.07 (s, 3 H, SiCH_3), 0.07 (s, 3 H, SiCH_3) ppm.

(4*R*,5*R*,9*R*,10*R*)-1,4-Bis(benzyloxy)-11-(*tert*-butyldimethylsilyloxy)-9,10-(2,2-dimethyl-1,3-dioxolane)-5-hydroxy-2,2-dimethylundecan-3,7-dione (26b): A stirred mixture of **25** (37 mg, 0.05 mmol), MeI (31 μL, 0.5 mmol), and $CaCO_3$ (25 mg, 0.25 mmol) in MeCN (1 mL)/H_2O (0.1 mL) was stirred at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2, dried with Na_2SO_4, filtered, and concentrated. Flash chromatography (EtOAc/cyclohexane, 1:5) gave **26b** (28 mg, 87%) as a yellow oil. ^1H NMR ($CDCl_3$): δ = 7.36–7.62 (m, 10 H, Ph-H), 4.60 (d, J = 4.3 Hz, 1 H, 4-H), 4.53 (d, J = 11.3 Hz, 1 H, CH_2Ph), 4.47 (s, 2 H, CH_2Ph), 4.43 (br. s, 1 H, OH), 4.42 (d, J = 11.3 Hz, 1 H, CH_2Ph), 4.27 (m, 1 H, 9-H), 3.81–3.76 (m, 1 H, 11-H), 3.71–3.65 (m, 2 H, 10-H, 11-H), 3.51 (s, 2 H, 1-H), 3.40 (d, J = 5.0 Hz, 1 H, 5-H), 2.79–2.69

(m, 4 H, 4-H and 6-H), 1.37 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 0.89 [s, 9 H, $SiC(CH_3)_3$], 0.07 (s, 3 H, $SiCH_3$), 0.07 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR ($CDCl_3$): δ = 213.7, 208.9, 137.7, 137.6, 128.4, 127.9, 127.7, 109.1, 82.0, 80.4, 77.6, 74.5, 73.4, 72.2, 68.4, 63.4, 48.5, 47.2, 44.8, 27.2, 26.9, 25.9, 22.1, 22.0, 18.3, –5.4 ppm. IR (neat): $\tilde{\nu}$ = 3490, 2920, 1710, 1090, 840 cm^{-1}. MS: calcd. for $C_{36}H_{54}O_8Si$ [M + H] 643.3667; found 643.3660.

Supporting Information (see footnote on the first page of this article): Experimental procedures for the synthesis of compounds **20**–**24** and NMR spectra of all compounds.

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