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# Relative Stereochemical Determination and Synthesis of the C17−C25 δ-Lactone Fragment of Hemicalide

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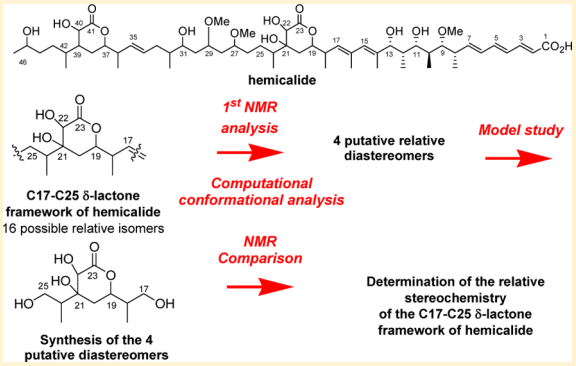
Supporting Information

**ABSTRACT:** Hemicalide is a novel marine metabolite polyketide distinguished by a unique mechanism of action. Because of insufficient quantities of purified material, this natural product has evaded complete stereochemical assignments. Recently, we have determined the relative stereochemistry of the C8−C13 hexad by synthesizing the C1−C13 fragment. Presently, we report the assignment of the C17−C25 δ-lactone fragment. NMR analysis of authentic hemicalide along with a computational conformation study allowed us to reduce the number of putative relative isomers from 16 to 4. Concise syntheses of the four candidate diastereomers were achieved using a common strategy based on a Dias aldehyde allylation reaction, an intramolecular Horner−Wadsworth−Emmons olefination, and a dihydroxylation reaction. Finally, thorough NMR comparisons enabled us to deduce the relative stereochemistry of the C1−C17 fragment with high certainty.




## INTRODUCTION

A new complex polyketide was recently isolated from extracts of the marine sponge *Hemimycale sp.*, collected in deep water around Torres Islands (Vanuatu) in the south Pacific, by French researchers of the CNRS-Pierre Fabre Laboratories joint unit in association with Institut de Recherche pour le Développement (IRD).[1] This new natural product, called hemicalide, was found to be a potent mitotic blocker and to display high antiproliferative potency against a panel of cancer cell lines at subnanomolar concentrations ($IC_{50}$ values ranging from 0.1 to 1 nM). Importantly, immunocytochemistry studies revealed that hemicalide acts by destabilizing the $\alpha/\beta$ microtubule network but the mechanism seems to be different from that observed with known antimitotic antitubulin agents. However, the remaining amount of hemicalide was not sufficient to support complementary pharmacological evaluation, and since harvesting the natural raw material is difficult and uncertain, chemical synthesis remained the only alternative way to pursue the research.

The planar structure of hemicalide **1** was fully elucidated through intensive NMR experiments.[1] The natural product comprises a 46-carbon backbone punctuated by 21 stereocenters (Figure 1). However, the stereochemical information was highly limited, since the very low extraction yield prevented any derivatization or degradation (less than 1 mg was isolated). The relative configurations of the stereogenic centers were therefore not assigned.

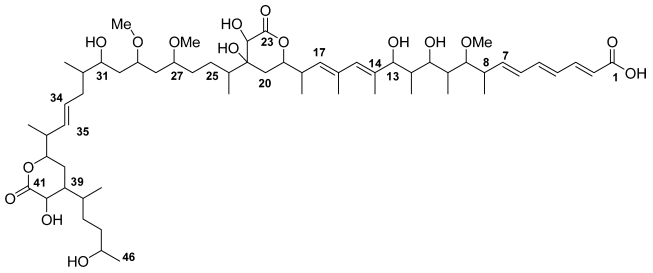


**Figure 1.** Structure of hemicalide **1**.

Recently, we achieved the relative stereochemical determination of the six contiguous stereogenic centers of the C8−C13 segment of hemicalide **1** by means of initial NMR analysis and subsequent synthesis of the six putative stereoisomers of model **2**, structurally close enough to the natural compound to allow NMR comparison (Figure 2).[2] A combination of these works led to the assignment of the C8−C13 motif as a syn-anti-anti-syn-syn stereohexad.[3]

Herein we report the relative structural determination of the C17−C25 α,β-dihydroxy-δ-lactone core appended with side arms substituted by methyl groups, with a high level of confidence. This work associates preliminary NMR experiments on the natural product, computational conformational analysis,

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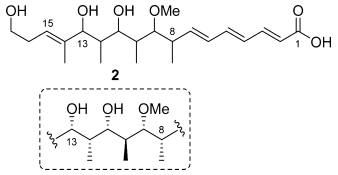


**Figure 2.** Model compound **2** and relative assignment of the C8−C13 stereocenters.[2].

and final synthesis of the appropriate four putative $\delta$-lactone models.

## RESULTS AND DISCUSSION

In order to establish the relative configuration of the five stereocenters of the C17−C25 $\delta$-lactone framework of **1**, NMR experiments were considered (Figure 3). NOESY analysis and

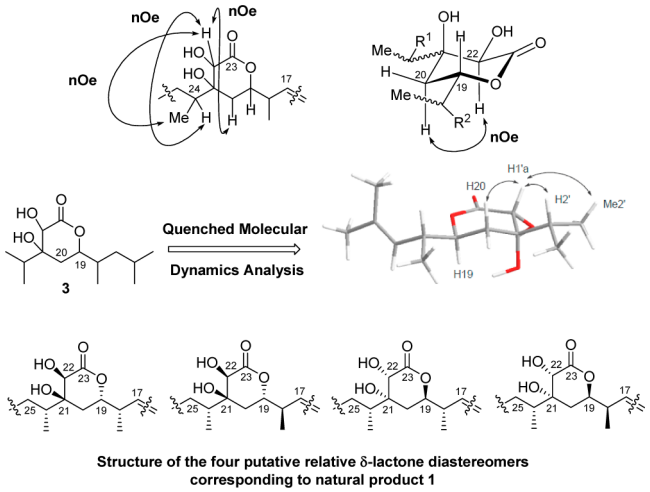



**Figure 3.** C17−C25 $\delta$-lactone framework of **1**: determination of the putative structures.

the characteristic $^3J(H_{19}-H_{20})$ coupling constant (11.3 Hz) were consistent with a chair conformation of this $\delta$-lactone with both hydroxy functions at C21 and C22 positions in a cis relationship and the chain at C19 in a relative trans orientation. Computational conformational analysis (Quenched Molecular Dynamic, Sybyl software) from model **3** did confirm this chair conformation.[4] As a result of these considerations, only 4 relative $\delta$-lactone diastereomers out of the 16 initially envisioned could potentially correspond to natural product **1** (Figure 3).

Therefore, we set out to synthesize the four $\delta$-lactone models (**4a**−**d**) in order to determine the relative stereochemistry of the C17−C25 $\delta$-lactone framework of hemicalide **1** (Figure 4). As previously done for the C8−C13 segment, these models were designed to be close enough to the natural compound to permit accurate NMR comparison.

The designed synthetic strategy could efficiently deliver the four isomers (**4a**−**d**) using common intermediates and featuring a limited number of steps (Scheme 1). The formation of these $\delta$-lactones was envisioned from corresponding $\alpha,\beta$-unsaturated lactones **8** by means of a syn-dihydroxylation reaction. Lactones **8** would be constructed from homoallylic alcohol **7**. For the synthesis of this intermediate and simultaneous control of the C19 stereocenter, a highly

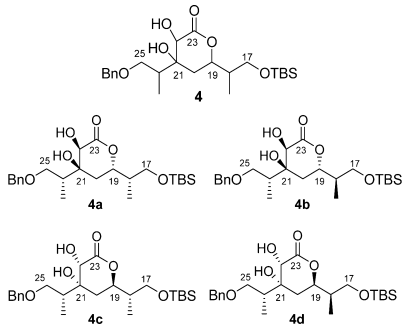
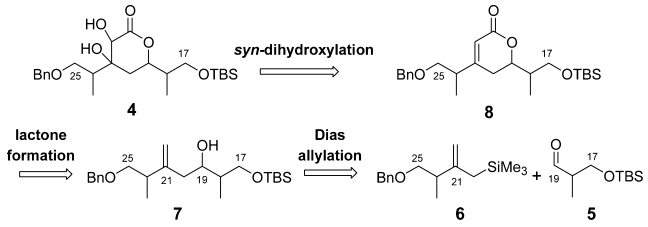



**Figure 4.** Structure of $\delta$-lactone models **4**.

**Scheme 1. $\delta$-Lactone Models 4: Retrosynthetic Strategy**

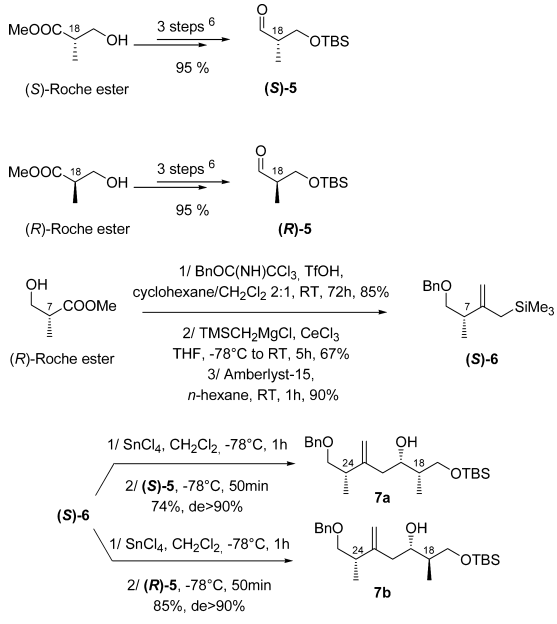



diastereoselective key Dias allylation reaction of aldehyde **5** by allylic silane **6** was selected.

To set up $\delta$-lactone stereocenters, we opted for a stereocontrolled tin-mediated allylation reaction. Initially reported by Dias, this reaction involves chiral aldehydes and a chiral allylic silane bearing an ethereal functionality as coupling partners and provides 1,4-syn homoallylic alcohols through 1,4-asymmetric induction.[5]

The preparation of diastereomeric homoallylic alcohols **7a,b**, precursors of lactones **4a,b**, is detailed in Scheme 2. (*S*)-and (*R*)-Roche esters were respectively converted into aldehydes (*S*)-**5** and (*R*)-**5**, by standard silylation of the hydroxy function, ester reduction, and subsequent Swern oxidation.[6] In the meantime, chiral allylsilane (*S*)-**6** was synthesized in a three-step sequence from (*R*)-Roche ester.[7] The organocerium

**Scheme 2. Synthesis of Homoallylic Alcohols 7a,b**





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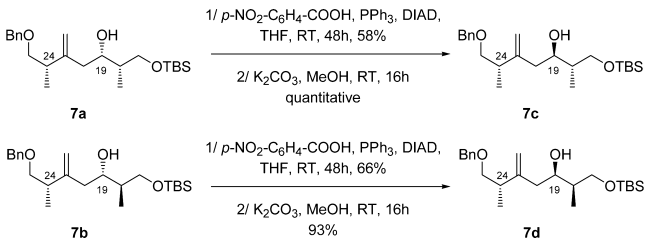
reagent generated from $CeCl_3$ and ((trimethylsilyl)methyl) magnesium chloride reacted with benzyl-protected (*R*)-Roche ester to afford the corresponding bis(silylmethyl)carbinol as an intermediate, which, after treatment with Amberlyst-15, led to the desired allylsilane (*S*)-**6** in 51% overall yield.[8] Then, to ensure transmetalation of allylsilane, (*S*)-**6** and $SnCl_4$ were mixed before addition of aldehydes (*S*)-**5** and (*R*)-**5**, respectively, providing expected homoallylic alcohols **7a,b** in high yields (74−85%) and diastereoselectivities (up to 90% de).[7]

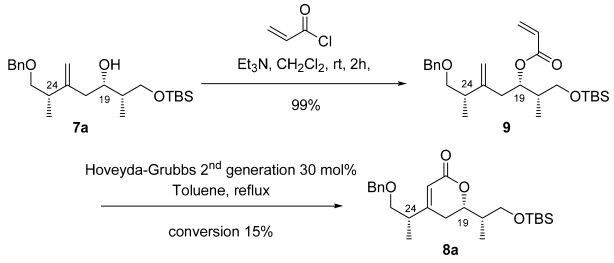
To obtain homoallylic alcohols **7c,d**, precursors of lactones **4c,d**, alcohols **7a,b** were subjected to an inversion of configuration at C19 under Mitsunobu conditions (Scheme 3).[9,10]

**Scheme 3. Synthesis of Homoallylic Alcohols 7c,d**




With access to the required homoallylic alcohols **7a−d** now reliable, the stage was set for the synthesis of lactones **4a−d**. As illustrated in Scheme 4, a ring closure metathesis (RCM) was

**Scheme 4. RCM Approach: Synthesis of Unsaturated δ-Lactone 8a**




first examined. This strategy would provide α,β-unsaturated δ-lactone **8a** from acrylate ester **9** (obtained by esterification of **7a**). Unfortunately, despite several attempts, the best conditions, i.e. slow addition of Hoveyda−Grubbs second-generation catalyst in refluxing toluene, afforded lactone **8a** with a mere conversion of 15%.[11] This modest performance could be attributed to steric considerations.[12]

Therefore, an alternative approach was suggested on the basis of an intramolecular Horner−Wadsworth−Emmons reaction. Synthesis of phosphonate **10a** under Steglich conditions[13] and subsequent ozonolysis to obtain ketone **11a** were achieved in high yields (Scheme 5).

However, an intramolecular Horner−Wadsworth−Emmons reaction from **11a** was impeded by difficulties associated with β-elimination as a competing side reaction, leading to a mixture of the desired lactone **8a** and α,β-unsaturated ketone **12a**.[14] Experimentally, several attempts were made to overcome this unfavorable elimination reaction, using different bases in THF (see Table 1).[15]

**Scheme 5. H-W-E Approach: Synthesis of δ-Lactone 4a**

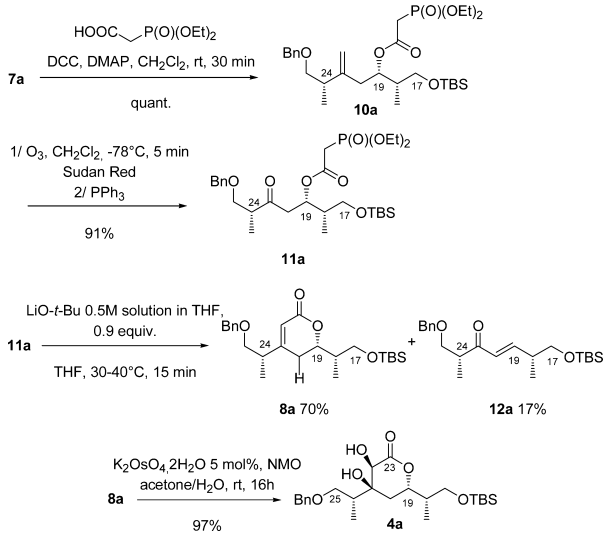



**Table 1. Optimization of the Intramolecular H-W-E Reaction from 11a**

| entry | base (equiv) | temp, °C | 8a:12a |
|---|---|---|---|
| 1 | NaH (0.9)[15a−c] | 0, room temp, or 40 | 20:80 |
| 4 | $K_2CO_3$ (1.5)[15d] | room temp | starting material |
| 5 | $Ba(OH)_2$ (1.5)[15e] | room temp | starting material |
| 6 | $LiClO_4$/DBU (1.5)[15f,g] | room temp | starting material |
| 7 | LiHMDS (1.0)[15h] | −10 | 0:100 |
| 8 | NaHMDS (1.0) | −10 | 0:100 |
| 9 | *n*-BuLi (1.0)[15h] | 40 | starting material |
| 10 | *t*-BuOLi (0.9)[15g] | 40 | 80:20[b] |

[a]Determined by $^1$H NMR analysis of crude mixtures. [b]**8a** isolated yield: 70%.

Finally, while the deprotonation was performed with freshly prepared lithium *tert*-butoxide in THF, lactone **8a** was isolated in a satisfactory 70% yield; however, side reactions could not be totally suppressed, since 17% of α,β-unsaturated ketone **12a** was still observed (Table 1 entry 10).[15g]

The final point of the sequence was the dihydroxylation of α,β-unsaturated lactone **8a** to lead to dihydroxylactone **4a** with both cis hydroxy functions at C21 and C22 in relative trans positions to the chain at C19. A diastereoselective dihydroxylation reaction in the presence of osmium tetroxide afforded the expected lactone **4a** in 97% yield (Scheme 5).[16] Lactone **4a** was obtained in 45.7% overall yield for eight steps.

Following a similar sequence, lactones **4b−d** were elaborated in 23.6−55.8% overall yield for 8 or 10 steps (due to Mitsunobu inversion of configuration at C19). Yields in key intermediates, phosphonates **11b−d**, and α,β-unsaturated lactones **8b−d** are highlighted in Scheme 6.

The relative structure of lactones **4a−d** (i.e., both hydroxy functions at C21 and C22 positions in a cis relationship and the chain at C19 in a relative trans orientation) was confirmed by NMR experiments (NOESY analysis and $^3J(H_{19}-H_{20})$ coupling constant values; see Figure 5 and the Supporting Information).

A direct NMR comparison between natural product **1** and the four synthesized lactones **4a−d** was performed.

A $^1$H NMR study was essential to discriminate the four lactones. The differences in the $^1$H NMR spectra are highlighted in Table 2 and Figure 6. In fact, $^1$H NMR data of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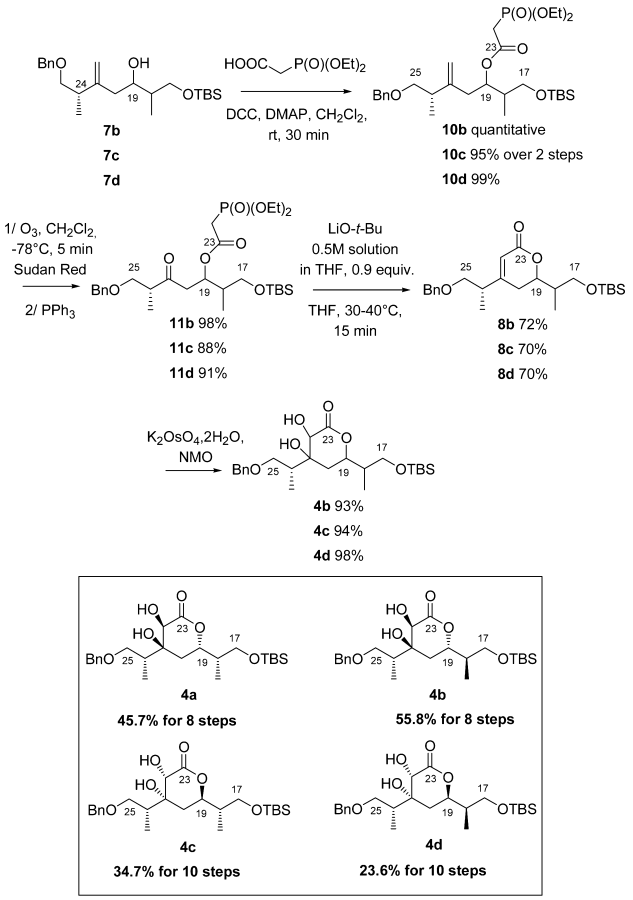
**Scheme 6. Synthesis of δ-Lactones 4b−d**



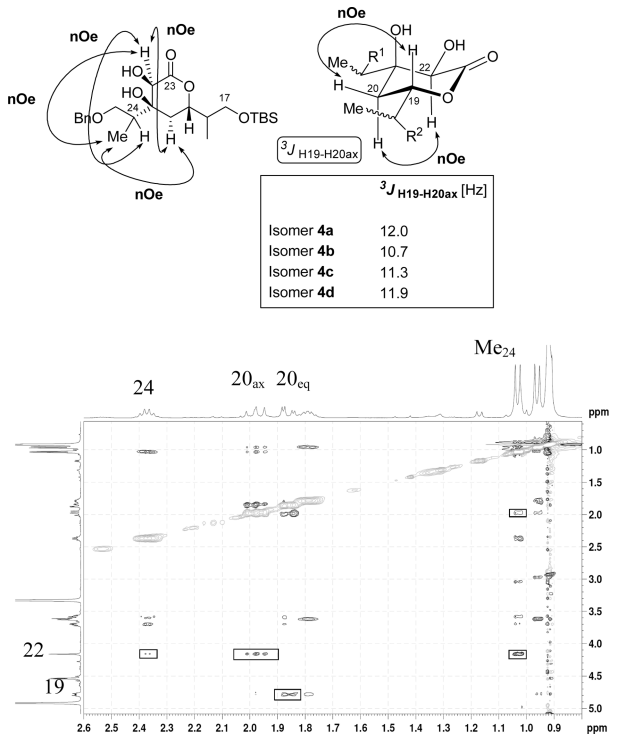




**Figure 5.** NMR analysis of δ-lactones **4a−d**: NOESY spectrum of δ-lactone **4d**.

**Table 2. Comparison of $^1$H NMR Data ($d_4$-Methanol, 500 MHz) for Hemicalide 1 and Isomers 4a−d**

| | δ(H), mult, $^3J$ (Hz) | |
|---|---|---|
| | H−C19 | H−C22 |
| hemicalide **1** | 4.42, ddd, 11.5, 7.5, 3.5 | 4.27, s |
| isomer **4a** | 4.76, dt, 12.0, 3.9 | 4.23, s |
| isomer **4b** | 4.62, ddd, 10.7, 6.7, 4.9 | 4.24, s |
| isomer **4c** | 4.63, ddd, 11.3, 6.7, 4.4 | 4.15, s |
| isomer **4d** | 4.77, dt, 11.9, 3.9 | 4.14, s |

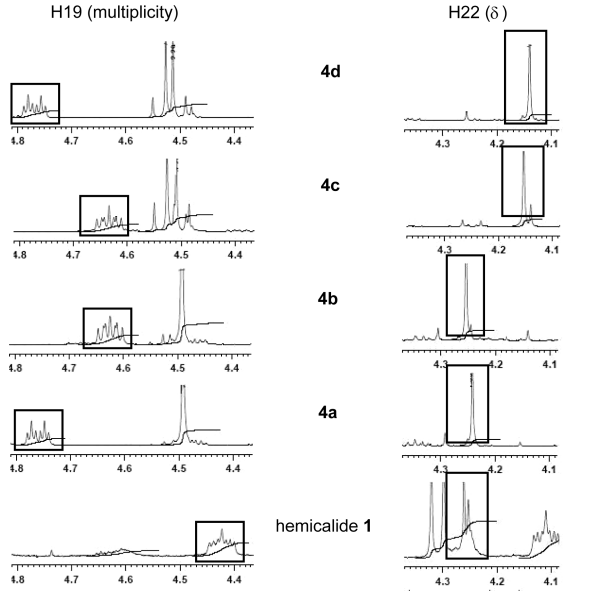



**Figure 6.** Comparison of the $^1$H NMR spectra for hemicalide **1** and isomers **4a−d**.

the two protons at the C20 position of the hemicalide are not accurately available and there is no proton at C21 (tertiary alcohol). Therefore, comparison was mainly localized at both C19 and C22 significant positions, the chemical shift of protons at these places being particularly dependent on the orientation of the δ-lactone substituents. $^1$H NMR data of protons at C22 and C19 are given for hemicalide **1** and δ-lactones **4a−d** in Table 2. The position at C22 is not affected by structural differences between the δ-lactone models and hemicalide **1**; therefore, the chemical shift of this proton can be considered as significant data to discriminate between different isomers. Thus, isomers **4a**,**b** (with a cis relationship between the C19 and C24 centers) are closest to hemicalide.

Concerning the H−C19 position, a direct comparison of chemical shifts seems irrelevant, given the structural differences between the natural molecule and models in this region. In contrast, the coupling constants at this level carry information on the relative configuration of different groups. Similarity in terms of multiplicity (ddd) and $^3J_{H-H}$ values between isomers **4b**,**c** (with an anti relationship between C18 and C19 centers) and hemicalide **1** could be observed, the other isomers **4a**,**d** having different multiplicities (dt).

Thus, it appeared that lactone **4b**, with a cis relationship between C19 and C24 and an anti orientation between C19 and C18, most closely matches the authentic natural product.

Comparison of $^{13}$C NMR data between isomers **4a−d** and hemicalide **1** was also performed but proved to be inconclusive (Figure 7). An initial comparison brings out differences of more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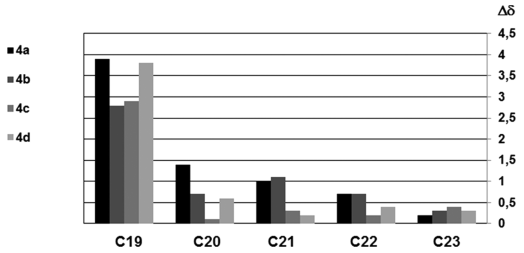


**Figure 7.** $\Delta\delta^{13}$C (ppm) between hemicalide 1 and lactones 20, 23, 26, and 29 for carbons 19−24.

than 2.5 ppm in the chemical shift of C19 between **1** and $\delta$-lactone models. This phenomenon could be explained by the C16−C17 double bond present in the natural molecule and absent in the models. Differences in chemical shifts at C20, C21, C22, and C23 between lactones **4a−d** and hemicalide **1** are shown in the figure. However, the $\Delta\delta$ values are not significant (most often less than 1 ppm); the four isomers have quite similar profiles.

## CONCLUSION

Despite significant technical challenges, the relative stereochemistry of the C17−C25 $\delta$-lactone fragment of hemicalide **1** has been elucidated. Prescreening of 16 putative stereoisomers by NMR analysis and computational conformation studies allowed us to focus our synthetic efforts on four likely candidates. A common and concise strategy involving Dias aldehyde allylation, Horner−Wadsworth−Emmons olefination, and dihydroxylation reaction was used to synthesize the four diastereomers of interest. On the basis of direct NMR spectral comparisons with the natural product, the best correlations were observed for $\delta$-lactone **4b**. The total synthesis of hemicalide using intermediate **4b** is ongoing and will be reported in due course.

## EXPERIMENTAL SECTION

**General Considerations.** All commercially available reagents and solvents were used without further purification. For reactions requiring anhydrous conditions, dry solvents were bought or freshly distillated prior to use (THF and $Et_2O$ over the sodium/benzophenone system, DCM and DMSO over calcium hydride, and MeOH and EtOH over magnesium). Unless otherwise noted, experiments were carried out under argon. Reactions were monitored by TLC (silica gel 60 $F_{254}$ plates) with detection by use of UV light (254 and 366 nm) or a phosphomolybdic acid solution in EtOH (5%) followed by heating at 100−110 °C. Purifications were performed by flash chromatography on silica gel (silica gel 60, 40−63 $\mu$m). $^1$H NMR spectra were recorded at 300, 400, and 500 MHz. Chemical shifts are given in ppm relative to the residual $^1$H solvent signal ($CDCl_3$, $\delta$ 7.26 ppm; $CD_3OD$, $\delta$ 3.31 ppm) as the internal reference. $^1$H NMR assignments were confirmed by 2D COSY spectra. The multiplicities given reflect apparent signal patterns. $^{13}$C NMR spectra were recorded at 100 and 125 MHz. Chemical shifts are given in ppm relative to the residual $^{13}$C solvent signal ($CDCl_3$, $\delta$ 77.0 ppm; $CD_3OD$, $\delta$ 49.0 ppm). $^{13}$C NMR assignments were confirmed by 2D HSQC spectra. Coupling constants ($J$) are given in Hz for all NMR spectroscopic data. IR spectra were recorded with a FT-IR spectrometer. Mass spectra were recorded with ESI-MS and ESI-TOF-HRMS instruments.

***δ*-Lactone 4a.** *(S)-(4-(Benzyloxy)-3-methyl-2-methylenebutyl)-trimethylsilane ((**S**)-6).* See ref 5a,b for the synthesis of the corresponding enantiomer (***R***)-**6**. A solution of methyl (*R*)-(−)-methyl D-$\beta$-hydroxyisobutyrate (10 mL, 90.2 mmol) in an anhydrous mixture of $CH_2Cl_2$ and cyclohexane (1/2, 120 mL) was cooled to 0 °C and treated with crude benzyl trichloroimidate (27.3 g, 108.1 mmol) and triflic acid (800 $\mu$L, 9.0 mmol) over 10 min. After 3 h, the mixture was warmed to 20 °C and stirred for 2 days. The solution was filtered through a pad of Celite and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 90/10) to give the expected (*R*)-methyl 3-(benzyloxy)-2-methylpropanoate (15.8 g, 85%) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.37−7.27 (m, 5H), 4.52 (s, 2H), 3.69 (s, 3H), 3.65 (dd, 1H, $J$ = 9.3, 1.7 Hz), 3.49 (dd, 1H, $J$ = 9.3, 4.9 Hz), 2.79 (qdd, 1H, $J$ = 7.1, 4.9, 1.7 Hz), 1.18 (d, 3H, $J$ = 7.1 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 175.3 (C), 138.1 (C), 128.3 (CH), 127.6 (CH), 127.5 (CH), 73.0 ($CH_2$), 71.9 ($CH_2$), 51.7 ($CH_3$), 40.1 (CH), 13.9 ($CH_3$).

In a three-neck 500 mL round-bottom flask, powdered $CeCl_3{\cdot}7H_2O$ (17.9 g, 48 mmol) was heated under vacuum (~3 mmHg) at 160 °C for 9 h with vigorous stirring, resulting in the formation of a white mobile solid. The reaction flask was then flushed with argon and cooled to room temperature before addition of THF (96 mL). The resulting uniform white suspension was stirred overnight at room temperature. After this time, this suspension was cooled to −78 °C and (trimethylsilyl)methylmagnesium chloride (1.3 M solution in THF, 37 mL, 48 mmol) was added dropwise, forming a brown-yellow suspension which was stirred at −78 °C for 1 h. The (*R*)-methyl 3-(benzyloxy)-2-methylpropanoate obtained above (2.0 g, 9.6 mmol) in THF (10 mL) was then added dropwise, and the resulting mixture was warmed gradually to room temperature. Upon complete consumption of starting material, the gray solution was cooled to 0 °C and quenched by addition of a saturated aqueous $NH_4Cl$ solution. The organic layer was separated, and the aqueous layer was further extracted with diethyl ether (2×). The combined organic extracts were washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo, affording the crude (*R*)-4-(benzyloxy)-3-methyl-1-(trimethylsilyl)-2-((trimethylsilyl)methyl)butan-2-ol (2.27 g, 67% yield). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.29−7.38 (m, 5H), 4.53 (s, 2H), 3.47 (dd, 1H, $J$ = 9.1, 4.8 Hz), 3.21 (dd, 1H, $J$ = 9.1, 8.1 Hz), 2.35−2.25 (m, 1H), 0.90−0.70 (m, 4H), 1.12 (d, 3H, $J$ = 7.1 Hz), 0.02 (s, 18H).

To a solution of the above alcohol (2.3 g, 6.5 mmol) in hexane (15 mL) at room temperature was added Amberlyst-15 (~0.5 equiv). The mixture was stirred until complete consumption of the starting material (maximum 1 h) before being filtered. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (cyclohexane/diethyl ether 98/2) to afford allylsilane (***S***)-**6** (1.54 g, 90%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.38−7.29 (m, 5H), 4.64 (s, 1H), 4.62 (s, 1H), 4.53 (s, 2H), 3.54 (dd, 1H, $J$ = 9.2, 4.8 Hz), 3.26 (dd, 1H, $J$ = 9.2, 8.1 Hz), 2.34−2.22 (m, 1H), 1.57 (m, 2H), 1.12 (d, 3H, $J$ = 6.6 Hz), 0.03 (s, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 149.9 (C), 138.8 (C), 128.4 (CH), 127.6 (CH), 127.5 (CH), 106.5 ($CH_2$), 75.0 ($CH_2$), 72.9 ($CH_2$), 40.9 (CH), 26.6 ($CH_2$), 17.0 ($CH_3$), −1.5 ($CH_3$). HRMS (TOF MS ES$^+$): calcd $m/z$ for $C_{16}H_{26}OSi$ (M + $Na^+$) 285.1651, found 285.1640. $[\alpha]_D^{22}$ = −12.5° ($c$ = 1.3, $CHCl_3$). IR (film, cm$^{-1}$): $\nu$ 3066, 2957, 2856, 1631, 1496, 1454, 1420, 1364, 1248, 1158, 1099, 958, 854, 735.

*(2S,3S,6S)-7-(Benzyloxy)-1-((tert-butyldimethylsilyl)oxy)-2,6-dimethyl-5-methyleneheptan-3-ol (**7a**).* See ref 5a,b for the synthesis of corresponding enantiomer ***ent*-7a**. Tin(IV) chloride (1.7 mL, 14.5 mmol) was slowly added to a cooled (−78 °C) solution of allylsilane **6** (3.8 g, 14.5 mmol) in $CH_2Cl_2$ (100 mL). The mixture was then stirred at −78 °C for 1 h. After this time, a solution of aldehyde **5**[6] (2.9 g, 14.5 mmol) in $CH_2Cl_2$ (5 mL) was added dropwise. The solution was stirred for 50 min at −78 °C and quenched by addition of triethylamine (~3 mL). The mixture was partitioned between $CH_2Cl_2$ and a saturated aqueous NaCl solution. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 97.5/2.5 to 90/10) in order to yield the desired homoallylic alcohol **7a** (4.1 g, 74% yield) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.35−7.27 (m, 5H), 4.93 (s, 1H), 4.91 (s, 1H), 4.51 (s, 2H), 3.97 (ddd, 1H, $J$ = 8.7, 5.8, 2.9 Hz), 3.68 (dd, 1H, $J$ = 9.8, 4.9 Hz), 3.64 (dd, 1H, $J$ = 9.8, 6.2 Hz), 3.50 (dd, 1H, $J$ = 9.1, 7.1 Hz), 3.35 (dd, 1H, $J$ = 9.1, 6.8 Hz), 2.50 (dqd, 1H, $J$ = 7.1, 6.9, 6.8 Hz), 2.23−2.17 (m, 2H), 1.72 (qddd, 1H, $J$ = 7.1, 6.2, 5.8, 4.9 Hz),


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1.06 (d, 3H, $J$ = 6.9 Hz), 0.93 (d, 3H, $J$ = 7.1 Hz), 0.90 (s, 9H), 0.06 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 149.3 (C), 138.4 (C), 128.3 (2CH), 127.6 (2CH), 127.5 (CH), 111.6 ($CH_2$,), 74.6 ($CH_2$), 73.0 ($CH_2$), 71.2 (CH), 67.4 ($CH_2$), 40.7 ($CH_2$), 39.2 (CH), 39.1 (CH), 25.9 ($3CH_3$), 18.2 (C), 17.5 ($CH_3$), 10.5 ($CH_3$), −5.5 ($CH_3$), −5.6 ($CH_3$). HRMS (TOF MS ES$^+$): calcd $m/z$ for $C_{23}H_{40}O_3Si$ (M + Na$^+$) 415.2644, found 415.2662. $[\alpha]_D^{22}$ = +8.5° ($c$ = 0.9, $CHCl_3$). IR (film): $\nu$ 3482, 2955, 2928, 2856, 1639, 1472, 1389, 1255, 1093, 894, 735 cm$^{-1}$.

*(2S,3S,6S)-7-(Benzyloxy)-1-((tert-butyldimethylsilyl)oxy)-2,6-dimethyl-5-methyleneheptan-3-yl Acrylate (**9**).* Alcohol **7a** (500 mg, 1.27 mmol) was dissolved in anhydrous $CH_2Cl_2$ (5 mL) at 0 °C. To this solution were added successively triethylamine (355 μL, 2.55 mmol) and acryloyl chloride (154 μL, 1.91 mmol). The mixture was warmed to room temperature, and the reaction was monitored by thin-layer chromatography. Upon total consumption of the starting material, the mixture was partitioned between $CH_2Cl_2$ (3×) and an saturated aqueous $NH_4Cl$ solution. The combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (cyclohexane/diethyl ether 100/0 to 80/20) to afford ester **9** as a colorless oil (568 mg, 99% yield). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.37−7.26 (m, 5H), 6.37 (dd, 1H, $J$ = 17.2, 1.6 Hz), 6.10 (dd, 1H, $J$ = 17.2, 10.4 Hz), 5.80 (dd, 1H, $J$ = 10.4, 1.6 Hz), 5.30 (td, 1H, $J$ = 7.0, 3.4 Hz), 4.88 (m, 2H), 4.56 (d, 1H, $J$ = 12.1 Hz), 4.51 (d, 1H, $J$ = 12.1 Hz), 3.51 (dd, 1H, $J$ = 9.3, 5.5 Hz), 3.50−3.42 (m, 2H), 3.36 (dd, 1H, $J$ = 9.3, 7.5 Hz), 2.53 (dqd, 1H, $J$ = 7.5, 7.0, 5.5 Hz), 2.41−2.35 (m, 2H), 1.99−1.88 (m, 1H), 1.12 (d, 3H, $J$ = 7.0 Hz), 0.95 (d, 3H, $J$ = 7.0 Hz), 0.90 (s, 9H), 0.03 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 165.6 (C), 147.8 (C), 138.7 (C), 130.1 ($CH_2$), 128.9 (2CH), 128.3 (2CH), 127.5 (CH), 127.4 (CH), 112.1 ($CH_2$), 74.5 ($CH_2$), 72.8 ($CH_2$), 72.6 (CH), 64.9 ($CH_2$), 39.1 (CH), 38.4 (CH), 37.6 ($CH_2$), 25.9 ($3CH_3$), 18.2 (C), 17.1 ($CH_3$), 10.9 ($CH_3$), −5.5 ($2CH_3$). HRMS (TOF MS ES$^+$) calcd $m/z$ for $C_{26}H_{42}O_4Si$ (M + Na$^+$) 469.2750, found 469.2764. $[\alpha]_D^{22}$ = +2.2° ($c$ = 1.1, $CHCl_3$). IR (film): $\nu$ 2929, 1723, 1193, 1095, 837 cm$^{-1}$.

*(2S,3S,6S)-7-(Benzyloxy)-1-((tert-butyldimethylsilyl)oxy)-2,6-dimethyl-5-methyleneheptan-3-yl 2-(Diethoxyphosphoryl)acetate (**10a**).* Diethylphosphonoacetic acid (205 μL, 1.27 mmol), DMAP (62 mg, 0.51 mmol), and DCC (263 mg, 1.27 mmol) were successively added to a solution of alcohol **7a** (200 mg, 0.51 mmol) in $CH_2Cl_2$ (10 mL) at room temperature. The mixture was stirred for 30 min and then concentrated in vacuo. The residue was taken up in a 1/1 mixture of $n$-hexane/diethyl ether and then filtered through a pad of Celite. The resulting yellow liquid was concentrated under reduced pressure. The crude ester was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 80/20 to 20/80) to afford phosphonate **17** (291 mg, 100% yield) as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.34−7.27 (m, 5H), 5.27 (td, 1H, $J$ = 7.0, 3.2 Hz), 4.88−4.85 (m, 2H), 4.53 (d, 1H, $J$ = 12.2 Hz), 4.48 (d, 1H, $J$ = 12.2 Hz), 4.20−4.03 (m, 4H), 3.48 (dd, 1H, $J$ = 9.2, 5.6 Hz), 3.47 (dd, 1H, $J$ = 10.0, 7.2 Hz), 3.43 (dd, 1H, $J$ = 10.0, 6.2 Hz), 3.34 (dd, 1H, $J$ = 9.2, 7.4 Hz), 2.92 (dd, 1H, $J$ = 14.4 Hz, $^1J_{P-H}$ = 21.6 Hz), 2.89 (dd, 1H, $J$ = 14.4 Hz, $^1J_{P-H}$ = 21.6 Hz), 2.48 (dqd, 1H, $J$ = 7.4, 6.9, 5.6 Hz), 2.35 (d, 2H, $J$ = 7.0 Hz), 1.87 (m, 1H), 1.33 (t, 6H, $J$ = 7.1 Hz), 1.09 (d, 3H, $J$ = 6.9 Hz), 0.92 (d, 3H, $J$ = 6.9 Hz), 0.87 (s, 9H), 0.01 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 165.2 (d, C, $^2J_{C-P}$ = 6.2 Hz), 147.6 (C), 128.3 (2CH), 127.5 (2CH), 127.4 (CH), 112.1 ($CH_2$), 74.5 ($CH_2$), 73.7 (CH), 72.8 ($CH_2$), 64.8 ($CH_2$), 62.5 (d, $2CH_2$, $^2J_{C-P}$ = 6.1 Hz), 39.0 (CH), 38.3 (CH), 37.6 ($CH_2$), 34.4 (d, $CH_2$, $^1J_{C-P}$ = 134.2 Hz), 25.8 ($3CH_3$), 18.2 (C), 17.1 ($CH_3$), 16.3 (d, $2CH_3$, $^3J_{C-P}$ = 6.2 Hz), 10.6 ($CH_3$), −5.5 ($2CH_3$). HRMS (TOF MS ES$^+$): calcd $m/z$ for $C_{29}H_{51}O_7PSi$ (M + Na$^+$) 593.3039, found 593.3052. $[\alpha]_D^{22}$ = +2.4° ($c$ = 2.2, $CHCl_3$). IR (film): $\nu$ 2930, 2856, 1735, 1271, 1098, 1027, 971, 832 cm$^{-1}$.

*(2S,3S,6R)-7-(Benzyloxy)-1-((tert-butyldimethylsilyl)oxy)-2,6-dimethyl-5-oxoheptan-3-yl 2-(Diethoxyphosphoryl)acetate (**11a**).* A stream of ozone was bubbled to a cooled (−78 °C) solution of phosphonate **10a** (3.43 g, 6.01 mmol) and Sudan III (small amount) in $CH_2Cl_2$ (80 mL) until the pink solution became colorless (ca. 5−10 min). Triphenylphosphine (2.36 g, 9.01 mmol) was then cautiously added, the cold bath was removed, and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the crude mixture was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 60/40 to 40/60) to afford ketone **11a** as a colorless oil (3.11 g, 91% yield). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.34−7.26 (m, 5H), 5.43 (ddd, 1H, $J$ = 9.8, 7.1, 4.1 Hz), 4.49 (d, 1H, $J$ = 11.9 Hz), 4.44 (d, 1H, $J$ = 11.9 Hz), 4.20−4.07 (m, 4H), 3.58 (dd, 1H, $J$ = 9.0, 7.8 Hz), 3.55−3.44 (m, 3H), 2.90−2.75 (m, 5H), 1.96−1.87 (m, 1H), 1.32 (m, 6H), 1.06 (d, 3H, $J$ = 7.0 Hz), 0.89 (d, 3H, $J$ = 6.9 Hz), 0.88 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 209.7 (C), 164.9 (d, C, $^2J_{C-P}$ = 6.4 Hz), 138.0 (C), 128.3 (2CH), 127.7 (2CH), 127.6 (CH), 73.3 ($CH_2$), 72.2 ($CH_2$), 71.9 (CH), 64.5 ($CH_2$), 62.6 (d, $2CH_2$, $^2J_{C-P}$ = 6.4 Hz), 46.5 (CH), 44.1 ($CH_2$), 38.7 (CH), 34.3 (d, $CH_2$, $^1J_{C-P}$ = 133.7 Hz), 25.8 ($3CH_3$), 18.2 (C), 16.3 (d, $2CH_3$, $^3J_{C-P}$ = 7.5 Hz), 13.2 ($CH_3$), 11.3 ($CH_3$), −5.5 ($2CH_3$). HRMS (TOF MS ES$^+$): calcd $m/z$ for $C_{28}H_{49}O_8PSi$ (M + Na$^+$) 595.2832, found 595.2864. $[\alpha]_D^{22}$ = −15.6° ($c$ = 2.6, $CHCl_3$). IR (film): $\nu$ 2931, 2856, 1736, 1259, 1098, 1027, 972, 837 cm$^{-1}$.

*(S)-4-((S)-1-(Benzyloxy)propan-2-yl)-6-((S)-1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-5,6-dihydropyran-2-one (**8a**).* Ketone **11a** (500 mg, 0.87 mmol) was dissolved in THF (20 mL) at 40 °C, and freshly prepared lithium *tert*-butoxide (0.5 M solution in THF, 1.57 mL, 0.79 mmol) was added very slowly. After the addition, the mixture was stirred for 15 min at 30−40 °C, before being quenched by addition of saturated aqueous $NH_4Cl$. The mixture was extracted with ethyl acetate (2×), the combined organic layers were dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 95/5 to 80/20) to yield lactone **8a** (256 mg, 70% yield) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.37−7.26 (m, 5H), 5.83 (d, 1H, $J$ = 2.3 Hz), 4.51 (d, 1H, $J$ = 12.0 Hz), 4.46 (d, 1H, $J$ = 12.0 Hz), 4.42 (ddd, 1H, $J$ = 12.5, 4.4, 3.7 Hz), 3.63 (dd, 1H, $J$ = 10.2, 6.6 Hz), 3.58 (dd, 1H, $J$ = 10.2, 5.5 Hz), 3.48−3.44 (m, 2H), 2.73−2.61 (m, 1H), 2.42 (ddd, 1H, $J$ = 17.4, 12.5, 2.3 Hz), 2.20 (dd, 1H, $J$ = 17.4, 3.7 Hz), 1.87 (m, 1H), 1.12 (d, 3H, $J$ = 7.0 Hz), 0.99 (d, 3H, $J$ = 7.0 Hz), 0.87 (s, 9H), 0.04 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 165.9 (C), 163.5 (C), 137.8 (C), 128.5 (2CH), 127.8 (2CH), 127.7 (CH), 115.6 (CH), 77.9 (CH), 73.2 ($CH_2$), 72.6 ($CH_2$), 64.2 ($CH_2$), 40.4 (CH), 39.5 (CH), 29.4 ($CH_2$), 25.9 ($3CH_3$), 18.2 (C), 15.6 ($CH_3$), 11.6 ($CH_3$), −5.5 ($2CH_3$). HRMS (TOF MS ES$^+$): calcd $m/z$ for $C_{24}H_{38}O_4Si$ (M + Na$^+$) 441.2437, found 441.2442. $[\alpha]_D^{22}$ = −42.7° ($c$ = 0.6, $CHCl_3$). IR (film): $\nu$ 2928, 2855, 1720, 1454, 1250, 1097, 836 cm$^{-1}$.

*(2R,6R,E)-1-(Benzyloxy)-7-((tert-butyldimethylsilyl)oxy)-2,6-dimethylhept-4-en-3-one (**12a**).* $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.35−7.26 (m, 5H), 6.85 (dd, 1H, $J$ = 15.9, 7.3 Hz), 6.19 (dd, 1H, $J$ = 15.9, 1.3 Hz), 4.52 (d, 1H, $J$ = 12.2 Hz), 4.47 (d, 1H, $J$ = 12.2 Hz), 3,71 (dd, 1H, $J$ = 9.1, 7.2 Hz), 3.55 (dd, 1H, $J$ = 9.6, 6.4 Hz), 3.52 (dd, 1H, $J$ = 9.6, 6.3 Hz), 3.45 (dd, 1H, $J$ = 9.1, 6.0 Hz), 3.21−3.09 (m, 1H), 2.56−2.45 (m, 1H), 1.12 (d, 3H, $J$ = 7.0 Hz), 1.05 (d, 3H, $J$ = 6.8 Hz), 0.88 (s, 9H), 0.03 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 202.3 (C), 150.0 (CH), 138.2 (C), 128.7 (CH), 128.3 (2CH), 127.6 (3CH), 73.2 ($CH_2$), 72.1 ($CH_2$), 66.9 ($CH_2$), 43.9 (CH), 39.4 (CH), 25.8 ($CH_3$), 18.3 (C), 15.6 ($CH_3$), 14.2 ($CH_3$), −5.4 ($2CH_3$). HRMS (TOF MS ES$^+$): calcd $m/z$ for $C_{22}H_{36}O_3Si$ (M + Na$^+$) 399.2331, found 399.2320.

*(3R,4S,6S)-4-((R)-1-(Benzyloxy)propan-2-yl)-6-((S)-1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-3,4-dihydroxy-tetrahydropyran-2-one (**4a**).* Potassium osmate(VI) dihydrate (11 mg, 0.03 mmol) was added to a solution of lactone **8a** (250 mg, 0.60 mmol) in acetone (2 mL) and $H_2O$ (2 mL) at room temperature. After stirring for 10 min, NMO (161 mg, 1.37 mmol) was added and the mixture was stirred overnight at room temperature. After this time, the dark brown solution was partitioned between ethyl acetate and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (cyclohexane/ethyl acetate 90:10 to 50:50) afforded required diol **4a** (263 mg, 97% yield) as a slightly yellow oil. $^1$H NMR (500 MHz, $CD_3OD$): $\delta$ 7.34−7.27 (m, 5H), 4.76 (dt, 1H, $J$ = 12.0, 3.9 Hz), 4.49 (s, 2H), 4.23 (s, 1H), 3.61 (dd, 1H, $J$ = 10.1, 7.1 Hz), 3.58 (dd, 1H, $J$ = 10.1, 6.5 Hz), 3.56 (dd, 1H, $J$ = 9.7, 5.8 Hz), 3.51 (dd, 1H, $J$ = 9.7, 5.5


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Hz), 2.31 (qdd, 1H, $J$ = 7.0, 5.8, 5.5 Hz), 1.98 (dd, 1H, $J$ = 14.5, 12.0 Hz), 1.84 (dd, 1H, $J$ = 14.5, 3.9 Hz), 1.76 (m, 1H), 1.05 (d, 3H, $J$ = 7.0 Hz), 0.91 (d, 3H, $J$ = 6.9 Hz), 0.90 (s, 9H), 0.07 (s, 6H). $^{13}$C NMR (125 MHz, $CD_3OD$): $\delta$ 176.8 (C), 139.6 (C), 129.4 (2CH), 128.9 (2CH), 128.7 (CH), 78.9 (CH), 75.4 (C), 74.3 ($CH_2$), 73.4 ($CH_2$), 73.2 (CH), 65.7 ($CH_2$), 41.3 (CH), 40.2 (CH), 33.6 ($CH_2$), 26.4 ($3CH_3$), 19.1 (C), 12.1 ($CH_3$), 11.4 ($CH_3$), −5.3 ($2CH_3$). HRMS (TOF MS ES$^+$): calcd $m/z$ for $C_{24}H_{40}O_6Si$ (M + Na$^+$) 475.2492, found 475.2482. $[\alpha]_D^{22}$ = +15.1° ($c$ = 3.7, $CHCl_3$). IR (film): $\nu$ 3448, 2955, 2928, 2856, 1729, 1471, 1462, 1252, 1102, 857, 777 cm$^{-1}$.

***δ*-Lactone 4b.** *(2R,3S,6S)-7-(Benzyloxy)-1-((tert-butyldimethylsilyl)oxy)-2,6-dimethyl-5-methyleneheptan-3-ol (**7b**).* See ref 5a,b for the synthesis of corresponding enantiomer ***ent*-7b**. Tin(IV) chloride (117 μL, 1.0 mmol) was slowly added to a cooled (−78 °C) solution of allylsilane **(*S*)-6** (262 mg, 1.0 mmol) in $CH_2Cl_2$ (8 mL). The mixture was then stirred at −78 °C for 60 min. After this time, a solution of aldehyde **(*R*)-5**[6] (202 mg, 1.0 mmol, 1.0 equiv) in $CH_2Cl_2$ (3 mL) was added dropwise. The solution was stirred for 50 min at −78 °C and quenched by addition of triethylamine (~0.5 mL). The mixture was partitioned between $CH_2Cl_2$ and a saturated aqueous NaCl solution. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 97.5/2.5 to 90/10) in order to yield homoallylic alcohol **7b** (334 mg, 85% yield) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.35−7.27 (m, 5H), 4.95 (s, 1H), 4.92 (s, 1H), 4.51 (s, 2H), 3.76−3.71 (m, 1H), 3.71 (dd, 1H, $J$ = 10.1, 3.7 Hz), 3.64 (dd, 1H, $J$ = 10.1, 5.9 Hz), 3.51 (dd, 1H, $J$ = 9.1, 7.4 Hz), 3.37 (dd, 1H, $J$ = 9.1, 6.6 Hz), 2.49 (dqd, 1H, $J$ = 7.4, 6.9, 6.6 Hz), 2.32 (dd, 1H, $J$ = 14.0, 3.3 Hz), 2.10 (dd, 1H, $J$ = 14.0, 9.3 Hz), 1.80−1.69 (m, 1H), 1.06 (d, 3H, $J$ = 6.9 Hz), 0.92 (d, 3H, $J$ = 7.0 Hz), 0.90 (s, 9H), 0.06 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 149.5 (C), 138.7 (C), 128.3 (2CH), 127.6 (2CH), 127.5 (CH), 111.7 ($CH_2$), 74.6 ($CH_2$), 73.0 ($CH_2$), 72.2 (CH), 66.4 ($CH_2$), 41.2 ($CH_2$), 40.1 (CH), 38.9 (CH), 25.9 ($3CH_3$), 18.2 (C), 17.6 ($CH_3$), 13.6 ($CH_3$), −5.5 ($2CH_3$). HRMS (TOF MS ES$^+$): calcd $m/z$ for $C_{23}H_{40}O_3Si$ (M + Na$^+$) 415.2644, found 415.2632. $[\alpha]_D^{22}$ = +8.8° ($c$ = 0.6, $CHCl_3$). IR (film): $\nu$ 3482, 2954, 2928, 2856, 1640, 1472, 1392, 1328, 1255, 1093, 894 cm$^{-1}$.

*(2R,3S,6S)-7-(Benzyloxy)-1-((tert-butyldimethylsilyl)oxy)-2,6-dimethyl-5-methyleneheptan-3-yl 2-(Diethoxyphosphoryl)acetate (**10b**).* Diethylphosphonoacetic acid (1.54 mL, 9.55 mol), DMAP (0.47 g, 3.82 mmol) and DCC (1.97 g, 9.55 mmol) were successively added to a solution of alcohol **7b** (1.50 g, 3.82 mmol) in $CH_2Cl_2$ (50 mL) at room temperature. The mixture was stirred for 30 min and then concentrated in vacuo. The residue was taken up in a 1/1 mixture of *n*-hexane and diethyl ether and the solution then filtered through a pad of Celite. The resulting yellow liquid was concentrated under reduced pressure. The crude ester was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 80:20 to 20:80) to afford desired diethoxyphosphorylacetate **10b** (2.18 g, 100% yield) as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.35−7.27 (m, 5H), 5.18 (ddd, 1H, $J$ = 8.9, 5.4, 3.2 Hz), 4.85 (s, 1H), 4.83 (s, 1H), 4.53 (d, 1H, $J$ = 11.9 Hz), 4.48 (d, 1H, $J$ = 11.9 Hz), 4.19−4.09 (m, 4H), 3.61 (dd, 1H, $J$ = 10.1, 6.2 Hz), 3.48 (dd, 1H, $J$ = 9.3, 5.7 Hz), 3.46 (dd, 1H, $J$ = 10.1, 4.7 Hz), 3.32 (dd, 1H, $J$ = 9.3, 7.5 Hz), 2.92 (dd, 1H, $J$ = 14.4 Hz, $^1J_{P-H}$ = 21.4 Hz), 2.87 (dd, 1H, $J$ = 14.4 Hz, $^1J_{P-H}$ = 21.4 Hz), 2.46 (dqd, 1H, $J$ = 7.5, 7.0, 5.7 Hz), 2.38 (dd, 1H, $J$ = 14.8, 3.2 Hz), 2.24 (dd, 1H, $J$ = 14.8, 8.9 Hz), 2.00 (m, 1H), 1.33 (t, 6H, $J$ = 7.1 Hz), 1.08 (d, 3H, $J$ = 7.0 Hz), 0.93 (d, 3H, $J$ = 7.0 Hz), 0.89 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 165.1 (d, C, $^2J_{C-P}$ = 6.3 Hz), 147.8 (C), 138.6 (C), 128.3 (2CH), 127.5 (2CH), 127.4 (CH), 111.7 ($CH_2$), 75.5 (CH), 74.4 ($CH_2$), 72.8 ($CH_2$), 64.4 ($CH_2$), 62.5 (d, $2CH_2$, $^2J_{C-P}$ = 6.3 Hz), 39.4 (CH), 39.0 (CH), 36.1 ($CH_2$), 34.3 (d, $CH_2$, $^1J_{C-P}$ = 134.3 Hz), 25.9 ($3CH_3$), 18.2 (C), 17.2 ($CH_3$), 16.3 (d, $2CH_3$, $^3J_{C-P}$ = 6.4 Hz), 12.6 ($CH_3$), −5.5 ($2CH_3$). HRMS (TOF MS ES$^+$): calcd $m/z$ for $C_{29}H_{51}O_7PSi$ (M + Na$^+$) 593.3039, found 593.3022. $[\alpha]_D^{22}$ = −1.5° ($c$ = 0.8, $CHCl_3$). IR (film): $\nu$ 2930, 2925, 2856, 1736, 1271, 1098, 1012, 971, 832, 735 cm$^{-1}$.

*(2R,3S,6R)-7-(Benzyloxy)-1-((tert-butyldimethylsilyl)oxy)-2,6-dimethyl-5-oxoheptan-3-yl 2-(Diethoxyphosphoryl)acetate (**11b**).* To a cooled (−78 °C) solution of the preceding phosphonate **10b** (2.18 g, 3.82 mmol) and Sudan III (small amount) in $CH_2Cl_2$ (55 mL) was bubbled a stream of ozone until the pink solution became colorless (ca. 5−10 min). Triphenylphosphine (1.50 g, 5.73 mmol) was then cautiously added, the cold bath was removed, and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the crude mixture was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 60/40 to 40/60) to afford the desired ketone **11b** as a colorless oil (2.14 g, 98% yield). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.36−7.25 (m, 5H), 5.44 (dt, 1H, $J$ = 7.4, 4.8 Hz), 4.49 (d, 1H, $J$ = 12.2 Hz), 4.44 (d, 1H, $J$ = 12.2 Hz), 4.19−4.08 (m, 4H), 3.60 (dd, 1H, $J$ = 9.2, 7.7 Hz), 3.57 (dd, 1H, $J$ = 10.2, 6.1 Hz), 3.47 (dd, 1H, $J$ = 10.2, 5.8 Hz), 3.44 (dd, 1H, $J$ = 9.2, 5.6 Hz), 2.90−2.80 (m, 5H), 2.04 (m, 1H), 1.33 (t, 6H, $J$ = 7.0 Hz), 1.06 (d, 3H, $J$ = 7.0 Hz), 0.91 (d, 3H, $J$ = 7.0 Hz), 0.87 (s, 9H), 0.02 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 209.5 (C), 164.8 (d, C, $^2J_{C-P}$ = 6.4 Hz), 138.0 (C), 128.4 (2CH), 127.6 (3CH), 73.2 ($CH_2$), 72.8 (CH), 71.9 ($CH_2$), 64.5 ($CH_2$), 62.5 (d, $2CH_2$, $^2J_{C-P}$ = 6.4 Hz), 46.7 (CH), 43.2 ($CH_2$), 38.6 (CH), 34.3 (d, $CH_2$, $^1J_{C-P}$ = 133.6 Hz), 25.8 ($3CH_3$), 18.2 (C), 16.3 (d, $2CH_3$, $^3J_{C-P}$ = 7.6 Hz), 13.3 ($CH_3$), 12.4 ($CH_3$), −5.5 ($CH_3$), −5.6 ($CH_3$). HRMS (TOF MS ES$^+$): calcd $m/z$ for $C_{28}H_{49}O_8PSi$ (M + Na$^+$) 595.2832, found 595.2821. $[\alpha]_D^{22}$ = −11.2° ($c$ = 1.7, $CHCl_3$). IR (film): $\nu$ 2931, 2925, 2856, 1734, 1259, 1096, 1027, 972, 841, 734 cm$^{-1}$.

*(S)-4-((S)-1-(Benzyloxy)propan-2-yl)-6-((R)-1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-5,6-dihydropyran-2-one (**8b**).* Ketone **11b** (500 mg, 0.87 mmol) was dissolved in THF (20 mL) at 40 °C, and freshly prepared lithium *tert*-butoxide (0.5 M solution in THF, 1.57 mL, 0.79 mmol) was added very slowly. After the addition, the mixture was stirred for 15 min at 30−40 °C, before being quenched by addition of saturated aqueous $NH_4Cl$. The mixture was extracted with ethyl acetate (2×), the combined organic layers were dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 95/5 to 80/20), and lactone **8b** (263 mg, 72% yield) was obtained as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.37−7.26 (m, 5H), 5.83 (d, 1H, $J$ = 1.9 Hz), 4.51 (d, 1H, $J$ = 12.1 Hz), 4.47 (d, 1H, $J$ = 12.1 Hz), 4.35 (ddd, 1H, $J$ = 11.9, 6.5, 4.3 Hz), 3.68 (dd, 1H, $J$ = 9.8, 5.2. Hz), 3.62 (dd, 1H, $J$ = 9.8, 5.5 Hz), 3.50−3.43 (m, 2H), 2.71−2.62 (m, 1H), 2.35 (ddd, 1H, $J$ = 17.4, 11.9, 1.9 Hz), 2.20 (dd, 1H, $J$ = 17.4, 4.3 Hz), 2.02 (qddd, 1H, $J$ = 7.0, 6.5, 5.5, 5.2 Hz), 1.11 (d, 3H, $J$ = 7.0 Hz), 0.95 (d, 3H, $J$ = 7.0 Hz), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 165.6 (C), 163.2 (C), 137.8 (C), 128.5 (2CH), 127.8 (2CH), 127.7 (CH), 115.6 (CH), 78.7 (CH), 73.2 ($CH_2$), 72.6 ($CH_2$), 63.9 ($CH_2$), 40.4 (CH), 39.3 (CH), 28.4 ($CH_2$), 25.9 ($3CH_3$), 18.2 (C), 15.6 ($CH_3$), 12.4 ($CH_3$), −5.5 ($2CH_3$). HRMS (TOF MS ES$^+$): calcd $m/z$ for $C_{24}H_{38}O_4Si$ (M + Na$^+$) 441.2437, found 441.2452. $[\alpha]_D^{22}$ = +35.1° ($c$ = 0.1, $CHCl_3$). IR (film): $\nu$ 2932, 2848, 1725, 1718, 1455, 1250, 1097, 937, 836 cm$^{-1}$.

*(3R,4S,6S)-4-((R)-1-(Benzyloxy)propan-2-yl)-6-((R)-1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-3,4-dihydroxytetrahydropyran-2-one (**4b**).* Potassium osmate(VI) dihydrate (11 mg, 0.03 mmol) was added to a solution of lactone **8b** (250 mg, 0.60 mmol) in acetone (2 mL) and $H_2O$ (2 mL) at room temperature. After the mixture was stirred for 10 min, NMO (160 mg, 1.37 mmol) was added and the mixture was stirred overnight at room temperature. After this time, the dark brown solution was partitioned between ethyl acetate (2×) and saturated aqueous NaCl. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (cyclohexane/ethyl acetate 90/10 to 50/50) afforded the desired diol **4b** (251 mg, 93% yield) as a slightly yellow oil. $^1$H NMR (500 MHz, $CD_3OD$): $\delta$ 7.34−7.26 (m, 5H), 4.62 (ddd, 1H, $J$ = 10.7, 6.7, 4.9 Hz), 4.49 (s, 2H), 4.24 (s, 1H), 3.68 (dd, 1H, $J$ = 10.1, 5.2 Hz), 3.64 (dd, 1H, $J$ = 10.1, 5.2 Hz), 3.57 (dd, 1H, $J$ = 9.7, 5.8 Hz), 3.49 (dd, 1H, $J$ = 9.7, 5.5 Hz), 2.34−2.28 (m, 1H), 1.93−1.84 (m, 3H), 1.04 (d, 3H, $J$ = 7.1 Hz), 0.92 (d, 3H, $J$ = 7.0 Hz), 0.90 (s, 9H), 0.06 (s, 6H). $^{13}$C NMR (125 MHz, $CD_3OD$): $\delta$ 176.7 (C), 139.6 (C), 129.4 (2CH), 128.9 (2CH), 128.7 (CH), 80.0 (CH), 75.3 (C), 74.2 ($CH_2$), 73.4 ($CH_2$), 73.2 (CH), 65.2 ($CH_2$), 41.6 (CH),


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40.2 (CH), 32.9 ($CH_2$), 26.4 ($3CH_3$), 19.1 (C), 12.6 ($CH_3$), 12.1 ($CH_3$), −5.3 ($CH_3$), −5.4 ($CH_3$). HRMS (TOF MS ES$^+$): calcd $m/z$ for $C_{24}H_{40}O_6Si$ (M + Na$^+$) 475.2492, found 475.2487. $[\alpha]_D^{22}$ = +7.8° ($c$ = 1.2, $CHCl_3$). IR (film): $\nu$ 3445, 2955, 2925, 2855, 1729, 1471, 1461, 1252, 1104, 854, 777, 734 cm$^{-1}$.

**δ-Lactone 4c.** *(2S,3R,6S)-7-(Benzyloxy)-1-((tert-butyldimethylsilyl)oxy)-2,6-dimethyl-5-methyleneheptan-3-ol (**7c**).* Alcohol **7a** (2.0 g, 5.1 mmol) was dissolved in THF (60 mL) at 0 °C. Triphenylphosphine (2.7 g, 10.2 mmol), *p*-nitrobenzoic acid (1.7 g, 10.2 mmol), and DIAD (2.0 mL, 10.2 mmol) were successively added to the solution. The mixture was stirred at 0 °C for 30 min then at room temperature for 2 days. After this time, saturated aqueous $NH_4Cl$ was added and the mixture was extracted with $CH_2Cl_2$ (2×). The combined organics were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (cyclohexane/diethyl ether 100/0 to 95/5) provided (2*S*,3*R*,6*S*)-7-(benzyloxy)-1-((*tert*-butyldimethylsilyl)oxy)-2,6-dimethyl-5-methyleneheptan-3-yl 4-nitrobenzoate (1.6 g, 58% yield). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.25 (d, 2H, $J$ = 8.6 Hz), 8.15 (d, 2H, $J$ = 8.6 Hz), 7.35−7.26 (m, 5H), 5.43 (ddd, 1H, $J$ = 10.1, 5.4, 3.1 Hz), 4.85 (s, 1H), 4.81 (s, 1H), 4.47 (s, 2H), 3.61 (dd, 1H, $J$ = 10.2, 6.2 Hz), 3.55 (dd, 1H, $J$ = 10.2, 5.9 Hz), 3.50 (dd, 1H, $J$ = 9.0, 6.0 Hz), 3.42 (dd, 1H, $J$ = 9.0, 6.1 Hz), 2.56−2.49 (m, 2H), 2.41 (dd, 1H, $J$ = 14.5, 10.1 Hz), 2.10 (qddd, 1H, $J$ = 7.0, 6.2, 5.9, 5.4 Hz), 1.06 (d, 3H, $J$ = 6.8 Hz), 0.98 (d, 3H, $J$ = 7.0 Hz), 0.88 (s, 9H,), 0.02 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 163.9 (C), 150.3 (C), 148.0 (C), 138.5 (C), 136.2 (C), 130.6 (2CH), 128.3 (2CH), 127.5 (2CH), 127.4 (CH), 123.5 (2CH), 112.3 ($CH_2$), 75.3 (CH), 75.1 ($CH_2$), 72.9 ($CH_2$), 64.6 ($CH_2$), 39.7 (CH), 38.9 (CH), 37.5 ($CH_2$), 25.9 ($3CH_3$), 18.2 (C), 16.9 ($CH_3$), 12.9 ($CH_3$), −5.5 ($2CH_3$). HRMS (TOF MS ES$^+$): calcd $m/z$ for $C_{30}H_{43}NO_6Si$ (M + Na$^+$) 564.2757, found 564.2768. $[\alpha]_D^{22}$ = +1.9° ($c$ = 1.4, $CHCl_3$). IR (film): $\nu$ 2929, 2856, 1735, 1704, 1652, 1257, 1097, 834 cm$^{-1}$.

Potassium carbonate (319 mg, 2.31 mmol) was added to a solution of the previous ester (1.25 g, 2.31 mmol) in methanol (40 mL) at room temperature. The mixture was stirred overnight, before being quenched by addition of saturated aqueous $NH_4Cl$ and extracted with $CH_2Cl_2$ (2×). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude alcohol **13** was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 97.5/2.5 to 90/10) but could not be separated from the *p*-nitrobenzoic acid methyl ester byproduct.

*(2S,3R,6S)-7-(Benzyloxy)-1-((tert-butyldimethylsilyl)oxy)-2,6-dimethyl-5-methyleneheptan-3-yl 2-(Diethoxyphosphoryl)acetate (**10c**).* Potassium carbonate (319 mg, 2.31 mmol) was added to a solution of the previous (2*S*,3*R*,6*S*)-7-(benzyloxy)-1-((*tert*-butyldimethylsilyl)oxy)-2,6-dimethyl-5-methyleneheptan-3-yl 4-nitrobenzoate (1.25 g, 2.31 mmol) in methanol (40 mL) at room temperature. The mixture was stirred overnight, before being quenched by addition of saturated aqueous $NH_4Cl$ and extracted with $CH_2Cl_2$ (2×). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude alcohol **7c** was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 97.5/2.5 to 90/10) but could not be separated from the *p*-nitrobenzoic acid methyl ester byproduct.

Diethylphosphonoacetic acid (921 μL, 5.73 mmol,), DMAP (280 mg, 2.29 mmol), and DCC (1182 mg, 5.73 mmol) were successively added to a solution of alcohol **7c** (900 mg, 2.29 mmol,) in $CH_2Cl_2$ (30 mL) at room temperature. The mixture was stirred for 30 min and then concentrated in vacuo. The residue was taken up in a 1/1 mixture of *n*-hexane and diethyl ether and then filtered through a pad of Celite. The resulting yellow liquid was concentrated under reduced pressure. The crude ester was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 90/10 to 40/60) to afford the required diethoxyphosphorylacetate **10c** (1.25 g, 95% over two steps) as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.34−7.29 (m, 5H), 5.16 (ddd, 1H, $J$ = 9.7, 5.0, 3.6 Hz), 4.86 (s, 1H), 4.84 (s, 1H), 4.51 (d, 1H, $J$ = 12.1 Hz), 4.46 (d, 1H, $J$ = 12.1 Hz), 4.21−4.09 (m, 4H), 3.60 (dd, 1H, $J$ = 10.1, 6.0 Hz), 3.45 (dd, 1H, $J$ = 10.1, 6.6 Hz), 3.42 (dd, 1H, $J$ = 9.1, 5.9 Hz), 3.28 (dd, 1H, $J$ = 9.1, 7.0 Hz), 2.91 (dd, 1H, $J$ = 14.4 Hz, $^1J_{P-H}$ = 21.4 Hz), 2.86 (dd, 1H, $J$ = 14.4 Hz, $^1J_{P-H}$ = 21.4 Hz), 2.47 (qddd, 1H, $J$ = 6.9, 6.6, 6.0, 5.0 Hz), 2.37 (dd, 1H, $J$ = 14.3, 3.6 Hz), 2.25 (dd, 1H, $J$ = 14.3, 9.7 Hz), 1.96 (m, 1H), 1.35−1.30 (m, 6H), 1.06 (d, 3H, $J$ = 6.9 Hz), 0.90 (d, 3H, $J$ = 6.9 Hz), 0.88 (s, 9H), 0.02 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 165.0 (d, C, $^2J_{C-P}$ = 6.3 Hz), 147.9 (C), 138.5 (C), 128.3 (2CH), 127.5 (2CH), 127.4 (CH), 111.9 ($CH_2$), 75.0 (CH), 74.9 (CH), 72.9 ($CH_2$), 64.4 ($CH_2$), 62.4 (d, $2CH_2$, $^2J_{C-P}$ = 6.2 Hz), 39.2 (CH), 38.8 (CH), 37.1 ($CH_2$), 34.2 (d, $CH_2$, $^1J_{C-P}$ = 134.9 Hz), 25.8 ($CH_3$), 18.2 (C), 16.9 ($CH_3$), 16.3 (d, $2CH_3$, $^3J_{C-P}$ = 6.2 Hz), 12.7 ($CH_3$), −5.4 ($CH_3$), −5.5 ($CH_3$). HRMS (TOF MS ES$^+$): calcd $m/z$ for $C_{29}H_{51}O_7PSi$ (M + Na$^+$) 593.3039, found 593.3064. $[\alpha]_D^{22}$ = −7.9° ($c$ = 2.5, $CHCl_3$). IR (film): $\nu$ 2930, 2927, 1732, 1274, 1098, 1012, 971, 837 cm$^{-1}$.

*(2S,3R,6R)-7-(Benzyloxy)-1-((tert-butyldimethylsilyl)oxy)-2,6-dimethyl-5-oxoheptan-3-yl 2-(Diethoxyphosphoryl)acetate (**11c**).* To a cooled (−78 °C) solution of the previous phosphonate **10c** (1.25 g, 2.19 mmol) and Sudan III (small amount) in $CH_2Cl_2$ (30 mL) was bubbled a stream of ozone until the pink solution became colorless (ca. 5−10 min). Triphenylphosphine (0.86 g, 3.29 mmol) was then cautiously added, the cold bath was removed and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the crude mixture was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 60/40 to 40/60) to afford ketone **11c** (1.1 g, 88% yield). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.34−7.26 (m, 5H), 5.46−5.39 (m, 1H), 4.49 (d, 1H, $J$ = 12.5 Hz), 4.44 (d, 1H, $J$ = 12.5 Hz), 4.19−4.09 (m, 4H), 3.62−3.54 (m, 2H), 3.52−3.42 (m, 2H), 2.92−2.70 (m, 5H), 2.05−1.97 (m, 1H), 1.35−1.29 (m, 6H), 1.05 (d, 3H, $J$ = 7.0 Hz), 0.90 (d, 3H, $J$ = 7.1 Hz), 0.87 (s, 9H), 0.02 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 209.9 (C), 164.9 (d, C, $^2J_{C-P}$ = 7.0 Hz), 138.0 (C), 128.4 (2CH), 127.6 (2CH), 127.5 (CH), 73.2 ($CH_2$), 72.9 (CH), 72.1 ($CH_2$), 64.5 ($CH_2$), 62.5 (d, $2CH_2$, $^2J_{C-P}$ = 6.4 Hz), 46.5 (CH), 43.2 ($CH_2$), 38.5 (CH), 34.2 (d, $CH_2$, $^1J_{C-P}$ = 133.9 Hz), 25.8 ($3CH_3$), 18.2 (C), 16.3 (d, $2CH_3$, $^3J_{C-P}$ = 6.3 Hz), 13.2 ($CH_3$), 12.4 ($CH_3$), −5.5 ($CH_3$), −5.6 ($CH_3$). HRMS (TOF MS ES$^+$): calcd $m/z$ for $C_{28}H_{49}O_8PSi$ (M + Na$^+$) 595.2832, found 595.2854. $[\alpha]_D^{22}$ = −4.3° ($c$ = 1.7, $CHCl_3$). IR (film): $\nu$ 2931, 2856, 1736, 1259, 1098, 1027, 972, 837 cm$^{-1}$.

*(R)-4-((S)-1-(Benzyloxy)propan-2-yl)-6-((S)-1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-5,6-dihydropyran-2-one (**8c**).* Ketone **11c** (500 mg, 0.87 mmol) was dissolved in THF (20 mL) at 40 °C, and freshly prepared lithium *tert*-butoxide (0.5 M solution in THF, 1.57 mL, 0.79 mmol) was added very slowly. After the addition, the mixture was stirred for 15 min at 30−40 °C, before being quenched by addition of saturated aqueous $NH_4Cl$. The mixture was extracted with ethyl acetate (2×), the combined organic layers were dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 95/5 to 80/20), and lactone **8c** (256 mg, 70% yield) was obtained. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.35−7.26 (m, 5H), 5.84 (d, 1H, $J$ = 2.3 Hz), 4.51 (d, 1H, $J$ = 12.2 Hz), 4.47 (d, 1H, $J$ = 12.2 Hz), 4.34 (ddd, 1H, $J$ = 12.2, 6.1, 3.5 Hz), 3.68 (dd, 1H, $J$ = 10.1, 5.4 Hz), 3.63 (dd, 1H, $J$ = 10.1, 5.5 Hz), 3.48−3.43 (m, 2H), 2.72−2.63 (m, 1H), 2.40 (ddd, 1H, $J$ = 17.6, 12.2, 2.3 Hz), 2.20 (dd, 1H, $J$ = 17.6, 3.5 Hz), 2.02 (qddd, 1H, $J$ = 7.0, 6.1, 5.5, 5.4 Hz), 1.12 (d, 3H, $J$ = 6.9 Hz), 0.95 (d, 3H, $J$ = 7.0 Hz), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 165.6 (C), 163.1 (C), 137.8 (C), 128.4 (2CH), 127.8 (2CH), 127.6 (CH), 115.8 (CH), 78.6 (CH), 73.2 ($CH_2$), 72.7 ($CH_2$), 63.8 ($CH_2$), 40.7 (CH), 39.3 (CH), 28.6 ($CH_2$), 25.8 ($3CH_3$), 18.2 (C), 15.0 ($CH_3$), 12.4 ($CH_3$), −5.5 ($CH_3$), −5.6 ($CH_3$). HRMS (TOF MS ES$^+$): calcd $m/z$ for $C_{24}H_{38}O_4Si$ (M + Na$^+$) 441.2437, found 441.2441. $[\alpha]_D^{22}$ = +40.3° ($c$ = 1.4, $CHCl_3$). IR (film): $\nu$ 2926, 2855, 1720, 1454, 1250, 1097, 836 cm$^{-1}$.

*(3S,4R,6R)-4-((R)-1-(Benzyloxy)propan-2-yl)-6-((S)-1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-3,4-dihydroxytetrahydropyran-2-one (**4c**).* Potassium osmate(VI) dihydrate (3 mg, 0.008 mmol) was added to a solution of lactone **8c** (50 mg, 0.12 mmol) in acetone (0.5 mL) and $H_2O$ (0.5 mL) at room temperature. After the mixture was stirred for 10 min, NMO (33 mg, 0.28 mmol) was added and the mixture was stirred overnight at room temperature. After this time, the dark brown solution was partitioned between ethyl acetate and


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saturated aqueous NaCl. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (cyclohexane/ethyl acetate 90/10 to 50/50) afforded diol **4c** (51 mg, 94% yield) as a pale oil. $^1$H NMR (500 MHz, $CD_3OD$): $\delta$ 7.34−7.26 (m, 5H), 4.63 (ddd, 1H, $J$ = 11.3, 6.7, 4.4 Hz), 4.54 (d, 1H, $J$ = 12.0 Hz), 4.50 (d, 1H, $J$ = 12.0 Hz), 4.15 (s, 1H), 3.70−3.64 (m, 3H), 3.58 (dd, 1H, J = 9.3, 6.0 Hz), 2.38−2.31 (m, 1H), 1.95−1.85 (m, 3H), 1.01 (d, 3H, $J$ = 7.0 Hz), 0.92 (d, 3H, $J$ = 7.0 Hz), 0.90 (s, 9H), 0.06 (s, 6H). $^{13}$C NMR (125 MHz, $CD_3OD$): $\delta$ 176.6 (C), 139.6 (C), 129.4 (2CH), 128.8 (2CH), 128.7 (CH), 79.9 (CH), 76.1 (C), 74.3 ($CH_2$), 72.8 ($CH_2$), 72.7 (CH), 65.2 ($CH_2$), 41.5 (CH), 39.4 (CH), 32.1 ($CH_2$), 26.4 ($3CH_3$), 19.1 (C), 13.3 ($CH_3$), 12.8 ($CH_3$), −5.2 ($CH_3$), −5.3 ($CH_3$). HRMS (TOF MS ES$^+$): calcd $m/z$ for $C_{24}H_{40}O_6Si$ (M + Na$^+$) 475.2492, found 475.2494. $[\alpha]_D^{22}$ = −15.9° ($c$ = 0.9, $CHCl_3$). IR (film): $\nu$ 3447, 2955, 2928, 2856, 1729, 1471, 1462, 1252, 777 cm$^{-1}$.

***δ*-Lactone 4d.** *(2R,3R,6S)-7-(Benzyloxy)-1-((tert-butyldimethylsilyl)oxy)-2,6-dimethyl-5-methyleneheptan-3-ol (**7d**).* Alcohol **7b** (750 mg, 1.91 mmol) was dissolved in THF (30 mL) at 0 °C. Triphenylphosphine (1 g, 3.82 mmol), *p*-nitrobenzoic acid (638 mg, 3.82 mmol), and DIAD (752 μL, 3.82 mmol) were successively added to the solution. The mixture was stirred at 0 °C for 30 min and then at room temperature for 2 days. After this time, saturated aqueous $NH_4Cl$ was added and the mixture was extracted with $CH_2Cl_2$ (2×). The combined organics were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (cyclohexane/diethyl ether 100/0 to 95/5) provided (2*R*,3*R*,6*S*)-7-(benzyloxy)-1-((*tert*-butyldimethylsilyl)oxy)-2,6-dimethyl-5-methyleneheptan-3-yl 4-nitrobenzoate (670 mg, 66% yield). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.27 (d, 2H, $J$ = 8.8 Hz), 8.15 (d, 2H, $J$ = 8.8 Hz), 7.35−7.27 (m, 5H), 5.52 (ddd, 1H, $J$ = 8.5, 5.6, 3.8 Hz), 4.87 (s, 1H), 4.84 (s, 1H), 4.49 (s, 2H), 3.51 (d, 2H, $J$ = 6.2 Hz), 3.46 (dd, 1H, $J$ = 9.0, 6.0 Hz), 3.32 (dd, 1H, $J$ = 9.0, 6.9 Hz), 2.59−2.48 (m, 2H), 2.45 (dd, 1H, $J$ = 14.1, 5.3 Hz), 2.01 (qtd, 1H, $J$ = 6.9, 6.2, 5.6 Hz), 1.09 (d, 3H, $J$ = 6.9 Hz), 1.02 (d, 3H, $J$ = 6.9 Hz), 0.87 (s, 9H), −0.01 (s, 3H), −0.02 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 164.0 (C), 147.7 (C), 138.5 (C), 136.2 (C), 130.5 (2CH), 128.3 (2CH), 127.5 (2CH), 123.5 (2CH), 112.4 ($CH_2$), 74.8 ($CH_2$), 74.2 (CH), 72.9 ($CH_2$), 65.0 ($CH_2$), 39.0 (CH), 38.9 (CH), 38.2 ($CH_2$), 25.8 ($3CH_3$), 18.2 (C), 17.0 ($CH_3$), 11.3 ($CH_3$), −5.6 ($2CH_3$). HRMS (TOF MS ES$^+$): calcd $m/z$ for $C_{30}H_{43}NO_6Si$ (M + Na$^+$) 564.2757, found 564.2749. $[\alpha]_D^{22}$ = −3.5° ($c$ = 2.6, $CHCl_3$). IR (film): $\nu$ 2932, 2856, 1735, 1705, 1656, 1257, 1097, 1054, 1027, 971, 837 cm$^{-1}$.

Potassium carbonate (171 mg, 1.24 mmol) was added to a solution of the previous ester (670 mg, 1.24 mmol) in methanol (25 mL) at room temperature. The mixture was stirred overnight, before being quenched by addition of $NH_4Cl$ and extracted with $CH_2Cl_2$ (2×). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 97.5/2.5 to 90/10) to furnish alcohol **7d** (453 mg, 93% yield). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.35−7.27 (m, 5H), 4.93 (s, 1H), 4.92 (s, 1H), 4.50 (s, 2H), 3.94 (m, 1H), 3.67 (dd, 1H, $J$ = 9.8, 4.5 Hz), 3.63 (dd, 1H, $J$ = 9.8, 4.4 Hz), 3.47 (dd, 1H, $J$ = 9.1, 6.6 Hz), 3.33 (dd, 1H, $J$ = 9.1, 6.9 Hz), 2.50 (quintd, 1H, $J$ = 6.9, 6.6 Hz), 2.20 (d, 2H, $J$ = 6.2 Hz), 1.73 (dqdd, 1H, $J$ = 7.4, 7.0, 4.5, 4.4 Hz), 1.10 (d, 3H, $J$ = 6.9 Hz), 0.92 (d, 3H, $J$ = 7.0 Hz), 0.89 (s, 9H), 0.06 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 149.4 (C), 138.4 (C), 128.3 (2CH), 127.6 (2CH), 127.5 (CH), 111.6 ($CH_2$), 74.8 ($CH_2$), 73.0 ($CH_2$), 71.8 (CH), 67.6 ($CH_2$), 40.7 ($CH_2$), 39.4 (CH), 39.1 (CH), 25.9 ($3CH_3$), 18.2 (C), 17.3 ($CH_3$), 10.4 ($CH_3$), −5.5 ($CH_3$), −5.6 ($CH_3$). HRMS (TOF MS ES$^+$): calcd $m/z$ for $C_{23}H_{40}O_3Si$ (M + Na$^+$) 415.2644, found 415.2654. $[\alpha]_D^{22}$ = −1.5° ($c$ = 2.1, $CHCl_3$). IR (film): $\nu$ 3481, 2954, 2928, 1642, 1472, 1351, 1255, 1093 cm$^{-1}$.

*(2R,3R,6S)-7-(Benzyloxy)-1-((tert-butyldimethylsilyl)oxy)-2,6-dimethyl-5-methyleneheptan-3-yl 2-(Diethoxyphosphoryl)acetate (**10d**).* Diethylphosphonoacetic acid (500 μL, 3.09 mmol), DMAP (151 mg, 1.24 mmol), and DCC (638 mg, 3.09 mmol) were successively added to a solution of alcohol **7d** (486 mg, 1.24 mmol) in $CH_2Cl_2$ (18 mL) at room temperature. The mixture was stirred for 30 min and then concentrated in vacuo. The residue was taken up in a 1/1 mixture of *n*-hexane and diethyl ether and the solution then filtered through a pad of Celite. The resulting yellow liquid was concentrated under reduced pressure. The crude ester was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 80/20 to 20/80) to afford diethoxyphosphorylacetate **10d** (703 mg, 99% yield) as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.35−7.26 (m, 5H), 5.29−5.22 (m, 1H), 4.86−4.85 (m, 2H), 4.52 (d, 1H, $J$ = 12.1 Hz), 4.47 (d, 1H, $J$ = 12.1 Hz), 4.20−4.08 (m, 4H), 3.49 (dd, 1H, $J$ = 9.1, 7.3 Hz), 3.49−3.40 (m, 2H), 3.30 (dd, 1H, $J$ = 9.1, 7.1 Hz), 2.92 (dd, 1H, $J$ = 14.4 Hz, $^1J_{P-H}$ = 24.1 Hz), 2.88 (dd, 1H, $J$ = 14.4 Hz, $^1J_{P-H}$ = 24.1 Hz), 2.52−2.43 (m, 1H), 2.40−2.25 (m, 2H), 1.88−1.82 (m, 1H), 1.33 (t, 6H, $J$ = 7.1 Hz), 1.08 (d, 3H, $J$ = 6.9 Hz), 0.93 (d, 3H, $J$ = 7.0 Hz), 0.87 (s, 9H), 0.01 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 165.1 (d, C, $^2J_{C-P}$ = 6.1 Hz), 147.7 (C), 138.8 (C), 128.3 (2CH), 127.5 (2CH), 127.4 (CH), 112.1 ($CH_2$), 74.7 ($CH_2$), 73.7 (CH), 72.9 ($CH_2$), 64.8 ($CH_2$), 62.5 (d, 2$CH_2$, $^2J_{C-P}$ = 6.3 Hz), 39.0 (CH), 38.8 (CH), 37.8 ($CH_2$), 34.0 (d, $CH_2$, $^1J_{C-P}$ = 136.5 Hz), 25.8 ($3CH_3$), 18.2 (C), 17.0 ($CH_3$), 16.3 (d, 2$CH_3$, $^3J_{C-P}$ = 6.2 Hz), 11.0 ($CH_3$), −5.5 ($2CH_3$). HRMS (TOF MS ES$^+$): calcd $m/z$ for $C_{29}H_{51}O_7PSi$ (M + Na$^+$) 593.3039, found 593.3034. $[\alpha]_D^{22}$ = −3.8° ($c$ = 1.2, $CHCl_3$). IR (film): $\nu$ 2930, 2925, 2856, 1736, 1271, 1098, 1011, 971, 837, 832, 735 cm$^{-1}$.

*(2R,3R,6R)-7-(Benzyloxy)-1-((tert-butyldimethylsilyl)oxy)-2,6-dimethyl-5-oxoheptan-3-yl 2-(Diethoxyphosphoryl)acetate (**11d**).* A stream of ozone was bubbled to a cooled (−78 °C) solution of the previous ester **10d** (1.18 g, 2.06 mmol) and Sudan III (small amount) in $CH_2Cl_2$ (28 mL) until the pink solution became colorless (ca. 5−10 min). Triphenylphosphine (0.81 g, 3.09 mmol) was then cautiously added, the cold bath was removed, and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the crude mixture was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 60/40 to 40/60) to afford ketone **11d** (1.07 g, 91% yield). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.35−7.26 (m, 5H), 5.43 (ddd, 1H, $J$ = 7.5, 5.2, 4.4 Hz), 4.49 (d, 1H, $J$ = 11.9 Hz), 4.44 (d, 1H, $J$ = 11.9 Hz), 4.20−4.08 (m, 4H), 3.59 (dd, 1H, $J$ = 9.1, 7.5 Hz), 3.52 (dd, 1H, $J$ = 10.2, 6.2 Hz), 3.48 (dd, 1H, $J$ = 10.2, 6.0 Hz), 3.45 (dd, 1H, $J$ = 9.1, 5.5 Hz), 2.90−2.80 (m, 5H), 1.91 (m, 1H), 1.33 (t, 6H, $J$ = 7.0 Hz), 1.07 (d, 3H, $J$ = 7.0 Hz), 0.92 (d, 3H, $J$ = 6.9 Hz), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 209.8 (C), 164.9 (d, C, $^2J_{C-P}$ = 6.2 Hz), 138.0 (C), 128.4 (2CH), 127.6 (2CH), 127.5 (CH), 73.2 ($CH_2$), 72.1 ($CH_2$), 72.0 ($CH_2$), 64.5 ($CH_2$), 62.5 (d, 2$CH_2$, $^2J_{C-P}$ = 6.2 Hz), 46.6 (CH), 43.8 ($CH_2$), 38.9 (CH), 34.3 (d, $CH_2$, $^1J_{C-P}$ = 133.7 Hz), 25.8 ($3CH_3$), 18.2 (C), 16.3 (d, 2$CH_3$, $^3J_{C-P}$ = 6.2 Hz), 13.3 ($CH_3$), 11.5 ($CH_3$), −5.5 ($2CH_3$). HRMS (TOF MS ES$^+$): calcd $m/z$ for $C_{28}H_{49}O_8PSi$ (M + Na$^+$) 595.2832, found 595.2852. IR (film): $\nu$ 2956, 2931, 2856, 1734, 1259, 1098, 1027, 971, 837 cm$^{-1}$.

*(R)-4-((S)-1-(Benzyloxy)propan-2-yl)-6-((R)-1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-5,6-dihydropyran-2-one (**8d**).* Ketone **11d** (500 mg, 0.87 mmol) was dissolved in THF (20 mL) at 40 °C, and freshly prepared lithium *tert*-butoxide (0.5 M solution in THF, 1.57 mL, 0.79 mmol) was added very slowly. After the addition, the mixture was stirred for 15 min at 30−40 °C, before being quenched by addition of saturated aqueous $NH_4Cl$. The mixture was extracted with ethyl acetate (2×), the combined organic layers were dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 95/5 to 80/20), and lactone **8d** (254 mg, 70% yield) was obtained. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.36−7.25 (m, 5H), 5.84 (d, 1H, $J$ = 2.3 Hz), 4.51 (d, 1H, $J$ = 11.9 Hz), 4.46 (d, 1H, $J$ = 11.9 Hz), 4.43 (ddd, 1H, $J$ = 12.6, 4.3, 3.3 Hz), 3.64 (dd, 1H, $J$ = 10.1, 7.0 Hz), 3.59 (dd, 1H, $J$ = 10.1, 5.3 Hz), 3.47−3.43 (m, 2H), 2.73−2.64 (m, 1H), 2.46 (ddd, 1H, $J$ = 17.3, 12.6, 2.3 Hz), 2.13 (dd, 1H, $J$ = 17.3, 3.3 Hz), 1.86 (dqdd, 1H, $J$ = 7.0, 6.9, 5.3, 4.3 Hz), 1.12 (d, 3H, $J$ = 7.0 Hz), 0.98 (d, 3H, $J$ = 6.9 Hz), 0.87 (s, 9H), 0.04 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 165.7 (C), 163.4 (C), 137.9 (C), 128.5 (2CH), 127.8 (2CH), 127.6 (CH), 115.8 (CH), 77.8 (CH), 73.2 ($CH_2$), 72.7 ($CH_2$), 64.2 ($CH_2$), 40.6 (CH), 39.5 (CH), 29.5 ($CH_2$), 25.9 ($3CH_3$), 18.2 (C), 15.0 ($CH_3$), 11.5 ($CH_3$), −5.5 ($2CH_3$). HRMS (TOF MS ES$^+$): calcd $m/z$ for $C_{24}H_{38}O_4Si$ (M +


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$Na^+$) 441.2437, found 441.2431. $[\alpha]_D^{22}$ = +33.9° (*c* = 1.4, $CHCl_3$). IR (film): $\nu$ 2928, 2855, 1720, 1454, 1254, 1098, 972, 837 $cm^{-1}$.

*(3S,4R,6R)-4-((R)-1-(Benzyloxy)propan-2-yl)-6-((R)-1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-3,4-dihydroxytetrahydropyran-2-one (**4d**).* Potassium osmate(VI) dihydrate (11 mg, 0.03 mmol) was added to a solution of lactone **8d** (250 mg, 0.60 mmol) in acetone (2 mL) and $H_2O$ (2 mL) at room temperature. After the mixture was stirred for 10 min, NMO (161 mg, 1.37 mmol) was added and the mixture was stirred overnight at room temperature. After this time, the dark brown solution was partitioned between ethyl acetate and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (cyclohexane/ethyl acetate 90/10 to 50/50) afforded diol **4d** (265 mg, 98% yield) as a slightly yellow oil. $^1H$ NMR (500 MHz, $CD_3OD$): $\delta$ 7.34−7.27 (m, 5H), 4.77 (dt, 1H, *J* = 11.9, 3.9 Hz), 4.54 (d, 1H, *J* = 11.9 Hz), 4.50 (d, 1H, *J* = 11.9 Hz), 4.14 (s, 1H), 3.68 (dd, 1H, *J* = 9.4, 6.0 Hz), 3.63−3.59 (m, 2H), 3.56 (dd, 1H, *J* = 9.4, 6.3 Hz), 2.35 (qdd, 1H, *J* = 7.1, 6.3, 6.0 Hz), 1.95 (dd, 1H, *J* = 14.2, 11.9 Hz), 1.84 (dd, 1H, *J* = 14.2, 3.9 Hz), 1.79−1.74 (m, 1H), 1.01 (d, 3H, *J* = 7.1 Hz), 0.94 (d, 3H, *J* = 6.9 Hz), 0.90 (s, 9H), 0.06 (s, 6H). $^{13}C$ NMR (125 MHz, $CD_3OD$): $\delta$ 176.7 (C), 139.6 (C), 129.6 (2CH), 129.4 (2CH), 128.7 (CH), 79.0 (CH), 76.2 (C), 74.3 ($CH_2$), 72.9 (CH), 72.8 ($CH_2$), 65.6 ($CH_2$), 41.2 (CH), 39.4 (CH), 32.8 ($CH_2$), 26.4 ($3CH_3$), 19.1 (C), 13.3 ($CH_3$), 11.5 ($CH_3$), −5.2 ($CH_3$), −5.3 ($CH_3$). HRMS (TOF MS ES$^+$): calcd *m*/*z* for $C_{24}H_{40}O_6Si$ (M + $Na^+$) 475.2492, found 475.2490. $[\alpha]_D^{22}$ = −19.5° (*c* = 0.8, $CHCl_3$). IR (film): $\nu$ 3448, 2954, 2927, 1729, 1472, 1462, 1257, 1101, 857, 777 $cm^{-1}$.

## ■ ASSOCIATED CONTENT

### Supporting Information

Figures giving full analyses of $^{13}C$ and $^1H$ NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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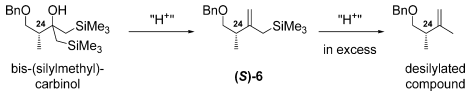


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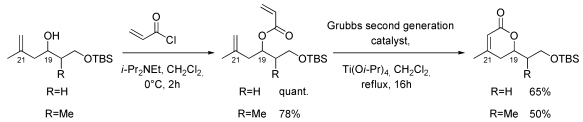


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