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Total Synthesis and Structural Elucidation of (−)-Maurenone

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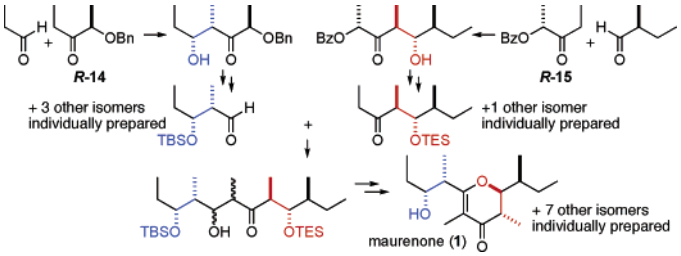

The total synthesis of (2*S*,3*S*)-2,3-dihydro-6-[(1′*S*, 2′*R*)-2-hydroxy-1-methylbutyl]-3,5-dimethyl-2-[(1″*S*)-1-methylpropyl]-4H-pyran-4-one **(3)**, the (−)enantiomer of the marine polypropionate, maurenone, was achieved in nine linear steps (13% overall yield) from (*R*)-2-benzylpentan-3-one ((*R*)-**14**) and (*R*)-2-benzoyloxypentan-3-one ((*R*)-**15**). Key fragments were synthesized using highly diastereoselective syn and anti boron aldol reactions and were coupled using a lithium-mediated aldol reaction. Trifluoroacetic acid-promoted cyclization/dehydration was then used to install the γ-dihydropyrone ring. Eight isomers of one enantiomeric series were synthesized by coupling two ketones with each of four aldehydes. Comparison of the ^{13}C NMR data for the eight isomers with that reported for maurenone established the relative stereochemistry of the natural product.

Introduction

Marine pulmonates of the genus *Siphonaria* are a rich source of diverse polyketide-derived natural products.[1] Examples containing oxygen heterocycles include siphonarin A and B[2] (spiroacetal and pyrone), muamvatin[3] (trioxaadamantane) denticulatin A and B[4] (hemiacetal), membrenone A−C (dihyropyrone),[5] and vallartanones A and B (dihydropyrone and pyrone).[6] Nearly all species examined have contained metabolites of polypropionate origin that appear to share a common biosynthesis with macrolide and polyether antibiotics.[7] In a number of cases, the stereochemistry of these natural products has been established by stereocontrolled synthesis of putative structures.[8]

Maurenone was isolated in 1986 by Faulkner and co-workers from specimens of the pulmonate mollusc *Siphonaria maura*, collected from Jaco Beach, Costa Rica.[9] The structure of maurenone was assigned, on the basis of ^{1}H and ^{13}C NMR data, to contain the relatively uncommon, tetra-substituted dihydropyrone moiety. The planar structure was determined, as shown in Figure 1, but the stereochemical information was limited and the configurations at C3, C4, and C10 were not assigned. Only an anti relationship between the C8 and C9 substituents was indicated by the large coupling constant $J_{8,9} = 12.3$ Hz.

Thus, considering the anti relationship between C8 and C9, there are 16 possible stereoisomers (8 pairs of enantiomers), 1 of which corresponds to maurenone. We set out to synthesize

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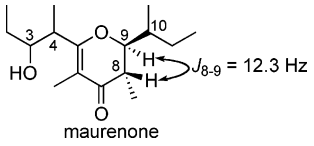


FIGURE 1. Structure of maurenone reported by Faulkner and coworkers.[9]

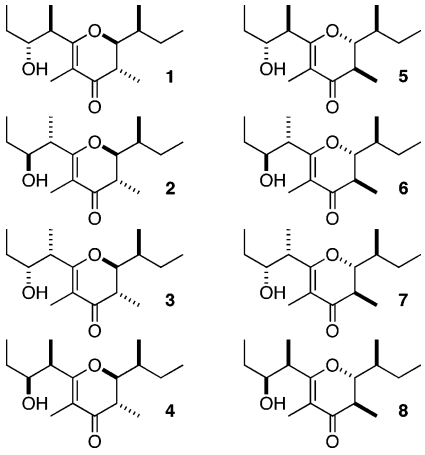


FIGURE 2. Possible isomers of maurenone (10*S* enantiomeric series).

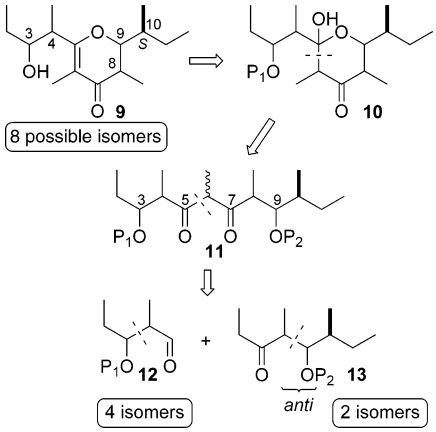
all eight possible isomers of one enantiomeric series to determine the stereochemistry of the natural product.[10] The series of compounds **1**−**8** (Figure 2) containing the *S* configuration at C10 was chosen because of the commercial availability of (*S*)-2-methylbutan-1-ol starting material.

Results and Discussion

We wished to employ a common strategy that could be used to generate the eight isomers using a number of common intermediates and a minimum number of steps. Scheme 1 outlines our retrosynthetic strategy for the maurenone structure with all required configurations at C3, C4, C8, and C9. Dihydropyrone **9** can be envisaged to arise by acid-catalyzed dehydration and deprotection of the corresponding hemiacetal **10**. Formation of hemiacetal **10** was proposed to occur by selective deprotection and cyclization of dione **11**. Dione **11** has pseudosymmetry but was preferentially prepared by an aldol/oxidation disconnection between C5 and C6 using aldehyde **12** and ketone **13**. Using this strategy, the eight isomers **1**−**8** of compound **9** can be prepared from four isomers of aldehyde **12** and two isomers of ketone **13**.

Our approach to the formation of required aldehydes **16**−**19** and ketones **20** and **21** is shown in Scheme 2. We proposed to exploit the high π-facial selectivity[11] in syn and anti aldol couplings of lactate-derived α-chiral ketones **14** and **15** to generate all of the required stereocenters. Enantiomeric anti

SCHEME 1. Retrosynthetic Analysis of Maurenone



aldehydes **16** and **17** are available from an aldol reaction between benzyloxy-protected ketones (*S*)-**15** and (*R*)-**15** and propanal (**22**) after hydrolysis and oxidative cleavage. Notably, the protecting group on the ketone dictates the enolate geometry,[11] and benzyl-protected ketones (*R*)-**14** and (*S*)-**14** can be used to prepare an enantiomeric pair of syn aldehydes **18** and **19**. Ketones **20** and **21** can be prepared by a similar anti selective aldol reaction between (*R*)-**15** and (*S*)-**15** and (*S*)-2-methylbutanal (**23**).

The synthesis of anti-anti ketone **20** (Scheme 3) began with an asymmetric aldol reaction between the dicyclohexylboron enolate of α-chiral ketone (*R*)-**15**[11] and α-chiral aldehyde **23** (obtained by Swern oxidation[12] of (*S*)-2-methylbutan-1-ol). The facial preference of the ketone controls the formation of C8 and C9 stereocenters in a mismatched double stereodifferentiating[13] anti aldol reaction to give compound **24** (83% yield, 90% ds). Silyl protection (TESOTf, 2,6-lutidine)[14] followed by controlled samarium diiodide (2−3 eqiv of SmI_2) mediated cleavage of benzoate ester **25**[11] gave ethyl ketone **20** in good yield (93%, 75% over three steps).

The alternative anti-syn ketone isomer **21** was synthesized via compounds **26** and **27** (73%, over three steps) using the same sequence as that described in Scheme 3, starting from (*S*)-2-benzoyloxypentan-3-one ((*S*)-**15**) (Scheme 4). In this case, the double stereodifferentiating reaction of α-chiral ketone (*S*)-**15** was matched with the Felkin[13] preference of chiral aldehyde **23**, giving aldol product **26** with no detectable minor isomer (83% yield, >95% ds).

The synthesis of anti aldehyde **16** (Scheme 5) began with a similar substrate-controlled anti aldol coupling between the dicyclohexylboron enolate of α-chiral ketone (*S*)-**15**[11] and propanal (**22**). In this case, the stereoselectivity with the achiral aldehyde is very high, giving aldol product **28** with no observed minor isomer. The generated alcohol was then protected as TBS ether **29**,[15] and the reduction of both ketone and ester functionalities with $LiBH_4$ gave 1,2-diol **30**. Oxidative cleavage using

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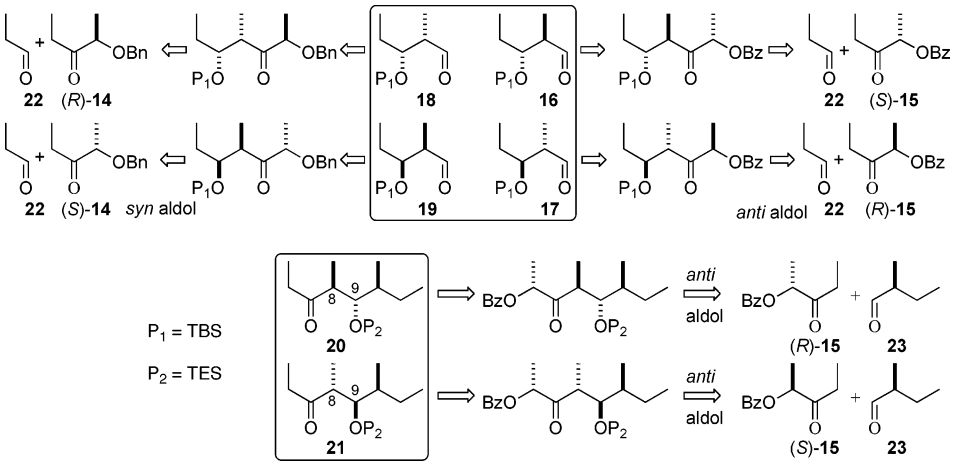
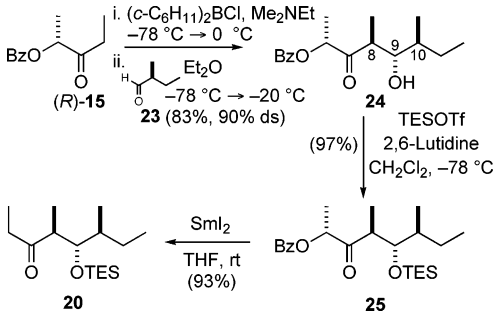
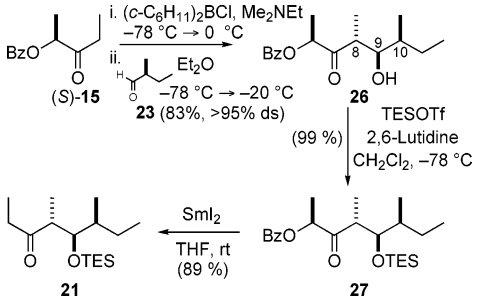
SCHEME 2. Proposed Synthesis of Aldehyde and Ketone Fragments



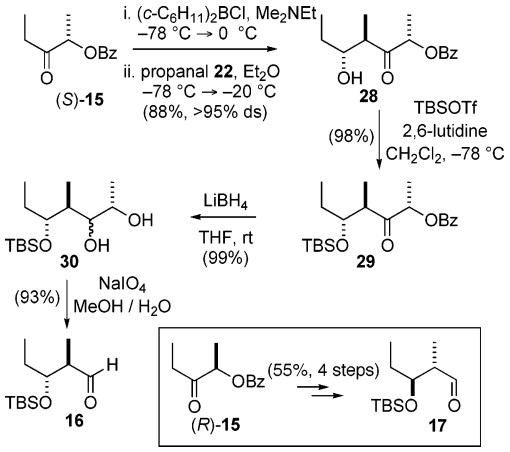
SCHEME 3. Synthesis of anti-anti Ketone



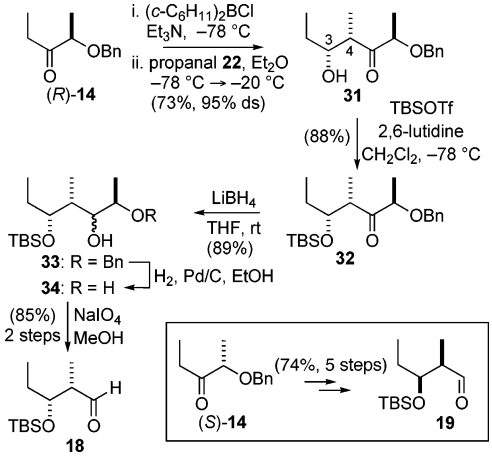
SCHEME 4. Synthesis of anti-syn Ketone



SCHEME 5. Synthesis of anti Aldehydes



SCHEME 6. Synthesis of syn Aldehydes



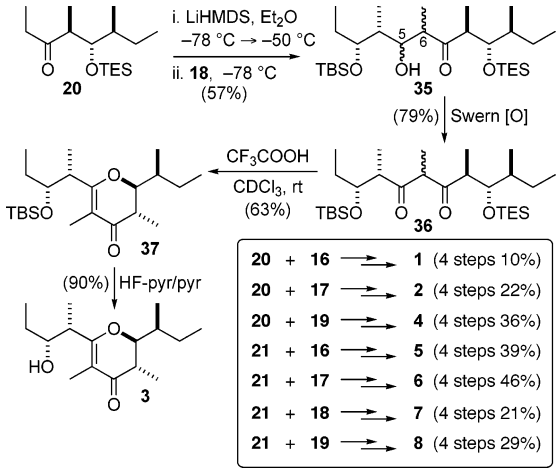
periodate[11] gave anti aldehyde **16** in good yield (79% over four steps). Synthesis of enantiomeric aldehyde **17** was performed in an identical manner, starting from (*R*)-benzoyloxypentan-3-one ((*R*)-**15**) (55% over four steps).

The synthesis of aldehyde **18** (Scheme 6) began with a substrate-controlled aldol coupling between the dicyclohexylboron enolate of α-chiral ketone (*R*)-**14**[11] and propanal (**22**), giving syn aldol product **31**. Notably, the change in the protecting group from Bz (in **15**) to Bn (in **14**) and the use of modified enolization conditions generates the cis enolate and thus syn aldol product **31**. Oxidative cleavage of this benzyl protected compound to the aldehyde requires a modified sequence. The hydroxyl was protected as TBS ether[15] **32**, and carbonyl reduction gave compound **33**. Hydrogenolysis of benzyl ether **33** gave 1,2-diol **34**, which was subsequently oxidized with $NaIO_4$ [11] to aldehyde **18** (85%, 49% over five steps). Synthesis of enantiomeric aldehyde **19** was performed in an identical manner, starting from (*S*)-benzylpentan-3-one ((*S*)-**14**) (74% over five steps).

The synthesis of all eight possible isomers of maurenone was now possible through the coupling of each of the two ketone isomers (**20** and **21**) with the four aldehyde isomers (**16**−**19**). Attempts to couple the titanium(IV) enolate ($TiCl_4$, *i*-Pr_2EtN)[16] of ketone **20** with aldehyde **18** proved troublesome because of the desilylation of the ketone during enolization. Fortunately, higher yields were achieved by employing a lithium enolate. The treatment of ketone **20** with lithium bis(trimethylsilyl)-amide[17] (Scheme 7) at −78 °C and the subsequent addition of

(16) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *J. Am. Chem. Soc.* **1995**, *117*, 9073.

SCHEME 7. Lithium-Mediated Aldol Coupling/Acid Promoted Cyclization−Dehydration



aldehyde **18** at −78 °C, which was stirred for 2 h, gave coupled product **35** in moderate yield with a moderate level of diastereoselectivity (74% ds). In this and other cases, the isomers could be separated and characterized. Ultimately, however, the stereochemistry at C5 and C6 was of little significance because they are both lost in subsequent steps. Thus, aldol adduct **35** was oxidized to corresponding dione **36** under Swern conditions.[12] Selective cleavage of triethylsilyl ether was achieved with trifluoroacetic acid, which also promoted spontaneous cyclization and dehydration to dihydropyrone **37**. Finally, liberation of the C3 alcohol with buffered HF-pyridine[18] gave desired product **3** in good yield (90%, 25% over four steps). Using this approach, synthesis of each of the possible isomers of maureone in the 10*S* enantiomeric series was accomplished using the same sequence as that described in Scheme 7.

Stereochemical assignment of the natural product was carried out by comparison of NMR spectra reported for the natural product with those obtained for various isomers **1**−**8**. There was little difference found in the ^{1}H spectrum from one isomer to the next, so our attention was turned to the ^{13}C NMR spectra. An inconsistency was immediately noted in that C7 for the natural product was reported[9] at $\delta = 208.2$ ppm, whereas for all isomers **1**−**8**, C7 was found to be in the range of $\delta = 195.5$−195.7 ppm. The chemical shift of $\delta = \sim 195$ ppm is consistent with previous findings for the presence of the γ-dihydropyrone carbonyl.[8] We thus assumed that the signal at 208.2 was misreported in the isolation paper.[19] In addition, only 15 of the required 16 carbon signals were reported,[9] and the signal for the quaternary C6 at $\delta = \sim 109$ ppm was missing.

Despite these inconsistencies, the differences in the ^{13}C NMR spectra were highlighted in Figures 3 and 4 by plotting the difference in chemical shift for each of the carbons[20] of isomers **1**−**8** compared to that reported in the original isolation. Figure 3 shows the comparison of the chemical shifts of compounds **5**−**8** derived from ketone **21**. There is a significant difference

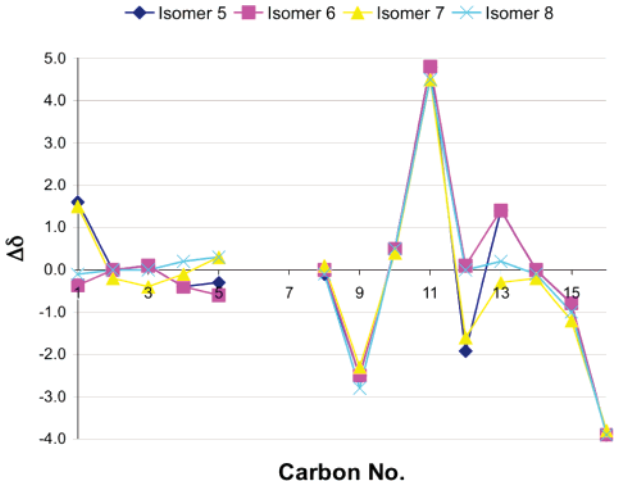


FIGURE 3. Difference in chemical shift ($\delta\Delta$) for isomers **5**−**8** derived from ketone **21**.

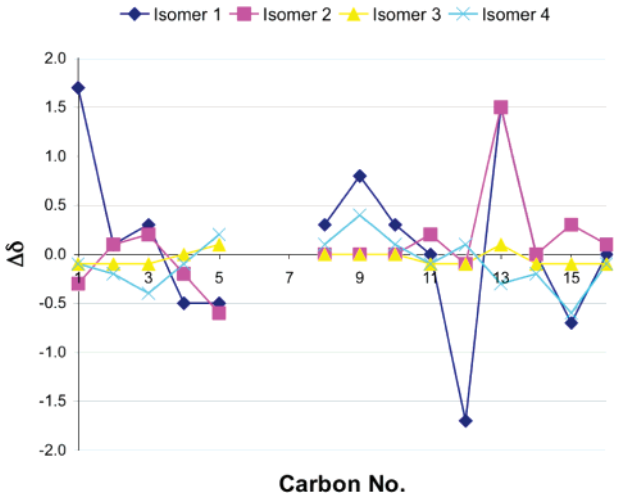


FIGURE 4. Difference in chemical shift ($\delta\Delta$) for isomers **1**−**4** derived from ketone **20**.

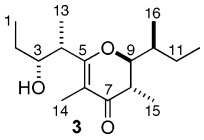
in the chemical shifts of a number of peaks for all four compounds, most notably at C9, C11, and C16. For these three carbons, the $\Delta\delta$ is 2.3−4.8 ppm for compounds **5**−**8**. On this basis, these structures were ruled out for the natural product maurenone.

A comparison with the compounds derived from ketone **20**, however, shows a much closer correlation with the natural product maurenone (Figure 2) with a maximum $\Delta\delta$ of 1.7 ppm. In this series, isomer **1** shows the largest differences for C1 ($\Delta\delta = 1.7$ ppm) and C12 ($\Delta\delta = -1.7$ ppm), and isomer **2** shows a large difference for C13 ($\Delta\delta = 1.7$ ppm) along with a number of other more minor deviations. On this basis, isomers **1** and **2** can be excluded, leaving the two syn aldehyde-derived isomers **3** and **4**. Small but consistent differences in the chemical shifts for isomer **4** are observed in a range of peaks. Isomer **3** alone shows an almost perfect correlation ($\Delta\delta \leq \pm 0.1$ ppm) with all of the peaks reported for maurenone,[9] and on this basis, the relative configuration of the natural product maurenone is assigned as shown for isomer **3**.

The ^{1}H and ^{13}C NMR data reported for the natural product and those obtained for isomer **3** are reported in Table 1 and show an excellent correlation. The mass spectral, IR, and UV data for isomer **3** were also consistent with those reported for

(17) Roush, W. R.; Bannister, T. D.; Wendt, M. D.; Jablonowski, J. A.; Scheidt, K. A. *J. Org. Chem.* **2002**, *67*, 4275.
(18) Robins, M. J.; Samano, V.; Johnson, M. D. *J. Org. Chem.* **1990**, *55*, 410.
(19) Attempts to obtain copies of the original spectra were unsuccessful; thus, no direct comparison with the original spectra was possible.
(20) The signals due to C6 and C7 were excluded from this comparison because of their absence from and apparent misreporting, respectively in the isolation report (ref 9).

TABLE 1. Comparison of the ^{1}H and ^{13}C NMR Data for Maurenone and Isomer 3 (the Structure Matching the Natural Product)



carbon no.	maurenone[a]		isomer 3[b]	
	δH, m, ^3J[Hz][c]	δC[c]	δH, m, ^3J[Hz][c]	δC[c]
1	0.95, t, 7.4	10.3	0.96, t, 7.2	10.2
2	1.40, m	28.0	1.49 and 1.39, m	27.9
3	3.65, ddd, 7.8, 6.5, 3.3	75.2	3.65, ddd, 8.4, 6.6, 3.6	75.1
4	2.78, dq, 6.9, 6.5	41.6	2.77, apt qn, 7.2	41.6
5		172.9		173.0
6				108.6
7		208.2		195.7
8	2.49, dq, 12.3, 7.0	40.6	2.49, dq, 12.3, 6.6	40.6
9	3.80, dd, 12.3, 3.0	87.0	3.77, dd, 12.3, 3.3	87.0
10	1.74, m	35.1	1.73, m	35.1
11	1.50, m	22.0	1.57 and 1.25, m	21.9
12	0.98, t, 7.5	11.8	0.94, t, 7.2	11.7
13	1.22, d, 6.9	13.2	1.20, d, 7.2	13.3
14	1.74, s	9.4	1.73, s	9.3
15	1.08, d, 6.9	10.7	1.08, d, 6.6	10.6
16	1.05, d, 6.9	16.2	1.03, d, 6.6	16.1

[a] Chemical shifts and coupling constants as reported in ref 9 (360 MHz). [b] NMR spectrometer (600 MHz, $CDCl_3$). Assignments assisted by ^{1}H−^{13}C HMBC, ^{1}H−^{13}C HMQC, and ^{1}H−^{1}H COSY. [c] Chemical shifts in ppm referenced to $CHCl_3$ at 7.26 ppm and to $CDCl_3$ at 77.0 ppm.

the natural product. Because no optical rotation was reported for the natural product, we were unable to assign the absolute configuration of the natural product.

Conclusions

In summary, a highly convergent synthesis of putative isomeric structures **1**−**8** for the natural product maurenone has been achieved by the reaction of ketones **20** and **21** with aldehydes **16**−**19**. This synthesis used lactate derived ketones (*R*)-**14** and (*S*)-**14** and (*R*)-**15** and (*S*)-**15** to generate four of the five required stereocenters in the final products. Comparison of the ^{1}H and ^{13}C NMR data reported for the natural product with those for the isomers enabled the assignment of the structure of the natural product as isomer **3**.

Experimental Section

(2*R*,4*S*,5*S*,6*S*)-2-Benzoyloxy-5-hydroxy-4,6-dimethyloctan-3-one (24). To a solution of dicyclohexylboron chloride (1.58 mL, 7.28 mmol) in Et_2O (19.5 mL) at −78 °C was added dimethylethylamine (0.95 mL, 8.73 mmol) dropwise, followed by ketone *R*-**15** (1.0 g, 4.85 mmol) in Et_2O (19.5 mL). The resulting milky white solution was slowly warmed to 0 °C and stirred for 2 h before cooling to −78 °C and adding aldehyde **23** (0.63 g, 7.28 mmol) dropwise. The solution was stirred for an additional 2 h at −78 °C before being placed in the freezer overnight. After this time, the solution was placed in a 0 °C bath and stirred for 30 min. The reaction was quenched by the addition of methanol (20 mL), pH 7 phosphate buffer (20 mL), and H_2O_2 (30%, 20 mL) at 0 °C. The solution was warmed to room temperature and stirred for 2.5 h before partitioning onto H_2O (300 mL) and extracting with CH_2Cl_2 (3 × 200 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The product was purified by column chromatography (100% CH_2Cl_2, R_f = 0.26) to yield 1.17 g (83%, 90% ds) of **24** as a white crystalline solid (mp 60−63 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10−8.07 (2H, m, Ar*H*), 7.62−7.57 (1H, m, Ar*H*), 7.49−7.44 (2H, m, Ar*H*), 5.46 (1H, q, J = 7.2 Hz, BzOC*H*), 3.60−3.53 (1H, m, C*H*OH), 3.08 (1H, apt qn, J = 6.9 Hz, C(=O)C*H*(CH_3)), 2.39 (1H, d, J = 7.2 Hz, O*H*), 1.62−1.48 (1H, m, C*H*(CH_3)CH_2), 1.57 (3H, d, J = 7.2 Hz, BzOCH(C*H*$_3$)), 1.27 (3H, d, J = 6.9 Hz, C(=O)CH(CH_3)), 1.31−1.13 (2H, m, C*H*$_2$$CH_3$), 0.93 (3H, d, J = 6.6 Hz, CH(C*H*$_3$)CH_2), 0.90 (3H, t, J = 7.1 Hz, CH_2C*H*$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 212.4, 133.4, 129.8, 129.5, 128.5, 78.2, 77.2, 74.7, 44.8, 37.1, 22.7, 16.3, 16.0, 14.8, 11.6; IR (film, cm^{-1}) 2967, 2936, 2876, 1718, 1453, 1316, 1268, 1118, 1006, 713, 667; $[\alpha]^{20}_D$ −43.1 (*c* 1.1, $CHCl_3$); HRMS (ESI) found 293.1747, $C_{17}H_{23}O_3H^+$ requires 293.1747; LREIMS 292 (1%), 235 (5%), 150 (25%), 113 (8%), 105 (100%), 97 (19%), 77 (34%), 57 (28%), 51 (12%).

(2*R*,4*S*,5*S*,6*S*)-2-Benzoyloxy-5-triethylsilyloxy-4,6-dimethyloctan-3-one (25). To a solution of alcohol **24** (0.42 g, 1.45 mmol) in CH_2Cl_2 (14.5 mL) at −78 °C was added 2,6-lutidine (0.67 g, 5.78 mmol) dropwise, followed immediately by TESOTf (0.98 mL, 4.35 mmol). The resulting solution was stirred at −78 °C for 1 h before quenching with $NaHCO_3$ (sat. aq, 30 mL). The product was partitioned onto H_2O (30 mL), extracted with CH_2Cl_2 (3 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo. The product was purified by column chromatography (50% mixed hexanes/CH_2Cl_2, R_f = 0.40), yielding 0.57 g (97%) of **25** as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10−8.06 (2H, m, Ar*H*), 7.59−7.53 (1H, m, Ar*H*), 7.46−7.41 (2H, m, Ar*H*), 5.44 (1H, q, J = 6.9 Hz, C*H*(CH_3)OBz), 3.94 (1H, dd, J = 9.0, 2.1 Hz, C*H*OTES), 3.11 (1H, dq, J = 9.0, 6.9 Hz, (C=O)C*H*(CH_3)), 1.57−1.39 (1H, m, CH(OTES)C*H*(CH_3)), 1.51 (3H, d, J = 6.9 Hz, BzOCH(C*H*$_3$)), 1.23−1.12 (2H, m, C*H*$_2$$CH_3$), 1.09 (3H, d, J = 6.9 Hz, (C=O)-CH(CH_3)), 0.95 (3H, d, J = 6.9 Hz; CH(C*H*$_3$)$CH_2$$CH_3$), 0.92 (9H, t, J = 7.9 Hz, Si(CH_2C*H*$_3$)$_3$), 0.89 (3H, t, J = 7.2 Hz, $CH_2$$CH_3$), 0.56 (6H, q, J = 7.2 Hz, Si(C*H*$_2$$CH_3$)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 209.2, 165.6, 133.1, 129.7, 128.3, 78.1, 75.0, 45.9, 38.9, 23.8, 15.6, 15.4, 14.2, 12.5, 6.9, 5.2; IR (film, cm^{-1}) 2962, 2914, 2878, 1724, 1454, 1382, 1316, 1301, 1268, 1177, 1116, 1059, 1027, 1006, 834, 739, 711, 687; $[\alpha]^{20}_D$ +7.1 (*c* 1.1, $CHCl_3$).

(4*S*,5*S*,6*S*)-5-*tert*-Butyldimethylsilyloxy-4,6-dimethyloctan-3-one (20). To a solution of benzoate **25** (0.82 g, 2.03 mmol) in THF (24.5 mL) and methanol (12.7 mL) at 0 °C was added (via a cannula) a solution of samarium diiodide (3−4 eqiv) in THF (0.1 M) until TLC analysis indicated reaction completion. The reaction was quenched by the addition of K_2CO_3 (sat. aq, 120 mL), and the product was extracted with Et_2O (3 × 150 mL). The combined extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The product was purified by column chromatography (40% CH_2Cl_2/mixed hexanes, R_f = 0.58), yielding 0.54 g (93%) of **20** as a clear, colorless oil. ^{1}H NMR (300 MHz, CDCl3) δ 3.83 (1H, dd, J = 7.8, 2.7 Hz, C*H*(OTES)), 2.78 (1H, apt qn, J = 7.2 Hz, C(=O)C*H*(CH_3)), 2.48 (2H, dq, J = 18.3, 7.2 Hz, CH_3C*H*$_2$C(=O)), 1.53−1.41 (1H, m, CH(OTES)-C*H*(CH_3)), 1.22−1.03 (2H, m, CH(CH_3)C*H*$_2$$CH_3$), 1.00 (3H, t, J = 7.2 Hz, C*H*$_3$$CH_2$C(=O)), 0.94 (3H, d, J = 7.2 Hz, C(=O)CH-(C*H*$_3$)), 0.91 (9H, t, J = 8.1 Hz, Si(CH_2C*H*$_3$)$_3$), 0.90−0.85 (6H, m, CH(C*H*$_3$)$CH_2$$CH_3$, CH($CH_3$)$CH_2$C*H*$_3$), 0.54 (6H, q, J = 8.1 Hz, Si(C*H*$_2$$CH_3$)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 214.5, 78.7, 49.6, 38.7, 36.7, 23.7, 15.7, 13.9, 12.3, 7.3, 6.9, 5.2; IR (film, cm^{-1}) 2962, 2939, 2879, 1721, 1460, 1414, 1378, 1240, 1133, 1115, 1090, 1058, 1008, 975, 835, 738; $[\alpha]^{20}_D$ +33.3 (*c* 1.1, $CHCl_3$); HRMS (ESI) found 287.2401, $C_{16}H_{34}O_2SiH^+$ requires 287.2401; LREIMS 257 (81%), 229 (14%), 201 (10%), 171 (65%), 143 (12%), 115 (14%), 103 (18%), 84 (43%), 75 (31%), 57 (100%), 51 (19%).

(2*R*,4*S*,5*R*)-2-Benzyloxy-5-hydroxy-4-methylheptan-3-one (31). To a solution of dicyclohexylboron chloride (1.24 mL, 5.72 mmol) in Et_2O (12 mL) at −78 °C was added triethylamine (0.95 mL, 6.8 mmol) dropwise, followed by ketone (*R*)-**14** (0.73 g, 3.79 mmol) in Et_2O (12 mmol). The resulting milky white solution was stirred at −78 °C for 2 h before the dropwise addition of propanal (**22**) (1.1 mL, 15.2 mmol). The solution was stirred for another 2 h at −78 °C before being placed in the freezer overnight. After this

time, the solution was placed in a 0 °C bath and stirred for 30 min. The reaction was quenched by the addition of methanol (12 mL), pH 7 phosphate buffer (12 mL), and H_2O_2 (30%, 12 mL)) at 0 °C. The solution was warmed to room temperature and stirred for 1 h before extracting the product with CH_2Cl_2 (3 × 100 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The product was purified by column chromatography (50% Et_2O/CH_2Cl_2, $R_f = 0.34$), yielding 0.69 g (73%, 95% ds) of adduct **31** as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.29 (5H, m, Ar*H*), 4.57 (1H, d, J = 11.7 Hz, OCH_AH$_B$Ph), 4.51 (1H, d, J = 11.7 Hz, OCH$_A$$H_B$Ph), 4.06 (1H, q, J = 6.9 Hz, C(=O)-C*H*(CH$_3$)O), 3.76 (1H, ddd, J = 8.1, 5.1, 3.0 Hz, CH$_3$CH$_2$C*H*(OH)), 3.01 (1H, dq, J = 7.2, 3.0 Hz, CH(OH)C*H*(CH$_3$)C(=O)), 2.31 (1H, s, OH), 1.56−1.28 (2H, m, CH$_3$CH_2), 1.38 (3H, d, J = 6.9 Hz, C(=O)CH(CH_3)O), 1.12 (3H, d, J = 7.2 Hz, CH(OH)CH(CH_3)-C(=O)), 0.93 (3H, t, J = 7.5 Hz, CH_3CH$_2$CH(OH)); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 217.1, 137.5, 128.5, 128.0, 127.8, 79.5, 72.5, 71.7, 44.8, 26.9, 17.3, 10.4, 10.0; IR (film, cm^{-1}) 3467, 2976, 2937, 2880, 1716, 1456, 1373, 1116, 1027, 973, 736, 698; $[\alpha]^{20}_D$ +18.1 (*c* 1.0, $CHCl_3$); HRMS (ESI) found 273.1471, $C_{15}H_{23}O_3Na^+$ requires 273.1416; LREIMS 181 (7%), 144 (10%), 135 (11%), 91 (100%), 69 (11%), 65 (12%), 59 (14%), 57.

(2*R*,4*S*,5*R*)-2-Benzyloxy-5-*tert*butyldimethylsilyloxy-4-methylheptan-3-one (32). To a solution of alcohol **31** (0.69 g, 2.77 mmol) in CH_2Cl_2 (30 mL) at −78 °C was added 2,6-lutidine (640 μL, 5.48 mmol) dropwise, followed immediately by TBSOTf (0.95 mL, 4.12 mmol). The resulting solution was stirred at −78 °C for 1 h before quenching with $NaHCO_3$ (sat. aq, 70 mL). The product was extracted with CH_2Cl_2 (3 × 70 mL), dried ($MgSO_4$), and concentrated in vacuo. The product was purified by column chromatography (20% mixed hexanes/CH_2Cl_2, $R_f = 0.50$), yielding 0.89 g (88%) of silyl ether **32** as a clear colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.27 (5H, m, Ar*H*), 4.56 (1H, d, J = 11.7 Hz, OCH_AH$_B$Ph), 4.52 (1H, d, J = 11.7 Hz, OCH$_A$$H_B$Ph), 4.08 (1H, q, J = 6.6 Hz, C(=O)C*H*(CH$_3$)OBn), 3.95 (1H, apt q, J = 5.7 Hz, C*H*(OTBS)), 3.08 (1H, apt qn, J = 6.9 Hz, CH(OTBS)-C*H*(CH$_3$)), 1.56−1.32 (2H, m, CH$_3$CH_2), 1.35 (3H, d, J = 6.6 Hz, C(=O)CH(CH_3)OBn), 1.06 (3H, d, J = 6.9 Hz, CH(OTBS)-CH(CH_3)), 0.87 (9H, s, SiC(CH_3)$_3$), 0.82 (3H, t, J = 7.5 Hz, CH_3CH$_2$), 0.03 (3H, s, Si(CH_3)$_A$(CH$_3$)$_B$), 0.00 (3H, s, Si(CH$_3$)$_A$-(CH_3)$_B$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 213.4, 137.7, 128.5, 127.9 (2), 79.0, 73.4, 71.3, 46.4, 28.1, 25.9, 18.1, 16.4, 12.7, 9.1, −4.1, −4.5; IR (film, cm^{-1}) 2960, 2933, 2898, 2883, 2858, 1720, 1473, 1465, 1255, 1120, 1105, 1046, 1030, 1006, 991, 835, 775, 736, 697, 667; $[\alpha]^{20}_D$ +39.0 (*c* 1.1, $CHCl_3$); HRMS (ESI) found 387.2327, $C_{21}H_{36}O_3SiNa^+$ requires 387.2326; LREISM 249 (40%), 173 (19%), 157 (23%), 143 (10%), 115 (21%), 91 (100%), 76 (18%), 73 (48%).

2-Benzyloxy-5-*tert*butyldimethylsilyloxy-4-methylheptan-3-ol (33). To a cooled (−78 °C) solution of ketone **32** (0.89 g, 2.44 mmol) in THF (30 mL) was added a solution of $LiBH_4$ (2M in THF, 7.3 mL, 14.6 mmol) dropwise. The reaction mixture was placed in an ice bath for 10 min before warming it slowly to room temperature. After stirring overnight, the solution was cooled to 0 °C before quenching by the addition of H_2O (50 mL). The product was extracted with Et_2O (4 × 50 mL). The combined Et_2O extracts were washed with brine (60 mL), dried ($MgSO_4$), and concentrated in vacuo. The product was purified by column chromatography (80% CH_2Cl_2/mixed hexanes, $R_f = 0.42$ and 0.36) to yield major isomer **33a** (0.65 g, 65%) and minor isomer **33b** (0.24 g, 24%) as clear, colorless oils. Major isomer (2*R*,3*S*,4*S*,5*R*) **(33a)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.25 (5H, m, ArH), 4.60 (1H, d, J = 12.0 Hz, OCH_AH$_B$Ph), 4.53 (1H, d, J = 12.0 Hz, OCH$_A$$H_B$Ph), 3.92 (1H, dt, J = 2.1, 7.2 Hz, C*H*(OTBS)), 3.80 (1H, dd, J = 3.6, 9.0 Hz, C*H*(OH)), 3.57 (1H, dq, J = 3.6, 6.3 Hz, C*H*(CH$_3$)OBn), 1.68 (1H, dqd, J = 3.0, 7.2, 10.2 Hz, CH(OTBS)C*H*(CH$_3$)), 1.52 (2H, m, CH$_3$CH_2CH(OTBS)), 1.20 (3H, d, J = 6.3 Hz, CH(OH)-CH(CH_3)OBn), 0.91 (9H, s, SiC(CH_3)$_3$), 0.87 (3H, t, J = 7.5 Hz, CH_3CH$_2$), 0.76 (3H, d, J = 7.2 Hz, CH(OTBS)CH(CH_3)), 0.10 (3H, s, Si(CH_3)$_A$(CH$_3$)$_B$), 0.08 (3H, s, Si(CH$_3$)$_A$(CH_3)$_B$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.6, 128.3, 127.6, 127.5, 75.8, 74.9, 73.6, 70.2, 37.8, 26.6, 25.9, 18.1, 12.8, 10.6, 9.8, −4.1, −4.6; IR (film, cm^{-1}) 3569, 3486, 2959, 2932, 2885, 2858, 1472, 1463, 1456, 1383, 1253, 1073, 1046, 1028, 1005, 983, 834, 775, 734, 697, 667; $[\alpha]^{20}_D$ +1.99 (*c* 1.5, $CHCl_3$); HRMS (ESI) found 267.2664, $C_{21}H_{38}O_3SiNa^+$ requires 267.2663; LREIMS 231 (7%), 201 (15%), 191 (19%), 181 (23%), 173 (46%), 159 (8%), 143 (7%), 133 (12%), 115 (14%), 91 (100%), 84 (26%), 75 (27%), 57 (20%), 55 (12%). Minor isomer (2*R*,3*R*,4*S*,5*R*) **(33b)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.27 (5H, m, Ar*H*), 4.67 (1H, d, J = 11.4 Hz, OCH_AH$_B$Ph), 4.45 (1H, d, J = 11.4 Hz, OCH$_A$$H_B$Ph), 3.64 (1H, apt q, J = 5.4 Hz, C*H*(OTBS)), 3.57−3.53 (2H, m, C*H*(OH), C*H*(CH$_3$)OBn), 1.74−1.63 (1H, m, CH(OTBS)C*H*(CH$_3$)), 1.63−1.50 (2H, m, CH$_3$CH_2), 0.90 (3H, d, J = 8.4 Hz, CH(OTBS)CH-(CH_3)), 0.89 (9H, s, SiC(CH_3)$_3$), 0.84 (3H, t, J = 7.5 Hz, CH$_3$CH$_2$), 0.05 (3H, s, Si(CH_3)$_A$(CH$_3$)$_B$), 0.03 (3H, s, Si(CH$_3$)$_A$(CH_3)$_B$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.4, 128.4, 127.8, 127.7, 77.1, 75.6, 75.2, 71.1, 38.0, 26.4, 25.9, 18.1, 15.5, 9.0, 8.9, −4.1, −4.5; IR (film, cm^{-1}) 3578, 2960, 2931, 2885, 2858, 1463, 1456, 1255, 1080, 1064, 1027, 1012, 1006, 836, 773, 697, 674, 667; $[\alpha]^{20}_D$ −19.8 (*c* 1.2, $CHCl_3$).

(2*R*,3*R*,4*S*,5*R*)-5-*tert*-Butylsilyloxy-4-methyl-heptan-2,3-diol (34a). To a solution of benzyl ether **33a** (0.58 g, 1.58 mmol) in ethanol (16 mL), under an atmosphere of nitrogen, was added palladium on activated carbon (10%, 60 mg). The flask was flushed with nitrogen followed by hydrogen, and the solution was stirred under an atmosphere of hydrogen for 2 h or until TLC analysis indicated that SM was consumed. The reaction mixture was diluted with ether (60 mL) and filtered through a pad of Celite and concentrated in vacuo to yield 0.44 g (99%) of **34a** as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77−3.67 (3H, m, C*H*(CH$_3$)OH, C*H*(OH), C*H*(OTBS)), 1.78−1.68 (1H, m, C*H*(CH$_3$)), 1.62−1.52 (2H, m, CH(OTBS)CH_2), 1.45 (3H, d, J = 6.3 Hz, CH-(CH$_3$)OH), 0.94 (3H, t, J = 7.2 Hz, CH$_2$CH_3), 0.91 (9H, s, OSiC-(CH_3)$_3$), 0.77 (3H, d, J = 7.2 Hz, CH(CH_3)), 0.11 (3H, s, OSi(CH_3)$_A$(CH$_3$)$_B$), 0.09 (3H, s, OSi(CH$_3$)$_A$(CH_3)$_B$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 79.1, 75.9, 68.8, 39.3, 25.8, 24.3, 18.4, 15.5, 12.4, 11.3, −4.5, −4.6; IR (film, cm^{-1}) 3423, 2961, 2934, 2885, 2860, 1473, 1464, 1385, 1255, 1130, 1105, 1069, 1046, 1016, 1003, 987, 870, 836, 776, 675, 667; $[\alpha]^{20}_D$ +20.6 (*c* 1.6, $CHCl_3$).

(2*R*,3*S*,4*S*,5*R*)-5-*tert*-Butylsilyloxy-4-methyl-heptan-2,3-diol (34b). Per the procedure for **34a**, benzyl ether **33b** (0.22 g, 5.88 mmol) was used to yield 0.15 g (91%,) of alcohol **34b** as a white semisolid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81−3.72 (2H, m, C*H*(OTBS), C*H*(CH$_3$)OH), 3.44 (1H, dd, J = 2.1, 7.2 Hz, C*H*(OH)), 2.87 (2H, br s, O*H*, O*H*), 1.75−1.66 (1H, m, CH(OH)C*H*(CH$_3$)), 1.60−1.50 (2H, m, CH(OTBS)CH$_2$), 1.14 (3H, d, J = 6.3 Hz, CH(CH_3)OH), 0.89 (9H, s, OSiC(CH_3)$_3$), 0.87 (3H, d, J = 7.2 Hz, CH(OH)CH(CH_3)), 0.83 (3H, t, J = 7.5 Hz, CH$_2$CH$_3$), 0.09 (6H, s, OSi(CH_3)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 79.4, 78.9, 68.9, 36.4, 27.0, 25.9, 18.8, 18.0, 9.8, 6.5, −3.7, −4.5; IR (film, cm^{-1}) 3401, 2961, 2932, 2885, 2859, 1473, 1464, 1381, 1362, 1256, 1132, 1103, 1078, 1051, 1014, 1006, 984, 860, 872, 836, 792, 773, 676, 667; $[\alpha]^{20}_D$ −11.5 (*c* 1.5, $CHCl_3$); HRMS (ESI) found 277.2195, $C_{14}H_{22}O_3SiH^+$ requires 277.2193; LREIMS 201 (35%), 173 (67%), 143 (17%), 133 (51%), 115 (41%), 75 (100%), 73 (64%), 57 (26%).

(2*S*,3*R*)-3-*tert*-Butyldimethylsilyloxy-2-methylpentanal (18). To a stirred solution of diols **34a** and **34b** (0.44 g, 1.58 mmol) in MeOH (16 mL) and H_2O (8 mL) at room temperature was added $NaIO_4$ (2.06 g, 9.6 mmol), and the resulting suspension was stirred for 15 min at room temperature. The reaction mixture was diluted with H_2O and extracted with Et_2O (3 × 60 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The product was purified by column chromatography (10% Et_2O/mixed hexanes, $R_f = 0.45$) to give 0.35 g (97%) of aldehyde **18** as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (1H, d, J = 0.9 Hz, CH(=O)), 4.03 (1H, dt, J = 3.6, 6.6 Hz, C*H*(OTBS)), 2.46 (1H, ddq, J = 0.9, 3.6, 6.9 Hz, CH(=O)C*H*(CH$_3$)), 1.64−1.45 (2H, m,

CH(OTBS)CH_2), 1.05 (3H, d, J = 6.9 Hz, CH(=O)CH(CH_3)), 0.88 (3H, t, J = 7.5 Hz, CH_2CH_3), 0.86 (9H, s, OSiC(CH_3)$_3$), 0.06 (3H, s, OSi(CH_3)$_A$(CH$_3$)$_B$), 0.03 (3H, s, OSi(CH$_3$)$_A$(CH_3)$_B$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 205.5, 73.4, 50.8, 27.4, 25.7, 18.0, 10.1, 7.6, −4.2, −4.7; IR (film, cm^{-1}) 2960, 2933, 2884, 2860, 1727, 1473, 1464, 1254, 1141, 1103, 1048, 1030, 1006, 837, 775, 667; $[\alpha]^{20}_D$ +53.7 (*c* 0.7, $CHCl_3$).

(3*S*,4*S*,5*S*,7*R*/*S*,9*R*/*S*,9*S*,10*R*)-10-*tert*-Butyldimethylsilyloxy-4-triethylsilyloxy-8-hydroxy-3,5,7,9-tetramethyldodeca-6-one (35). To a solution of ketone **20** (105 mg, 0.368 mmol) in THF (0.74 mL) at −78 °C was added a solution of lithium bis(trimethylsilyl)-amide (1 M in THF, 552 μL, 0.552 mmol) dropwise. The resulting yellow solution was stirred at −78 °C for 30 min and then warmed to −50 °C for 30 min. The solution was then cooled to −78 °C, and aldehyde **18** (127 mg, 0.552 mmol) was added. The resulting solution was stirred at −78 °C for 2 h. The reaction was quenched by the addition of pH 7 phosphate buffer solution (2 mL), and the organics were extracted with Et_2O (5 × 5 mL). The combined extracts were washed with brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The product was purified by column chromatography (5% Et_2O/hexanes, R_f = 0.21, 0.13 and 0.05) to yield 108 mg (57%) of aldol adduct **35** as a mixture of diastereomers (0.74:0.08:0.18) and clear, colorless oils. **35a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.04−3.98 (2H, m, C*H*(OH), C*H*(OTBS)), 3.87 (1H, dd, J = 8.1, 3.0 Hz, C*H*(OTES)), 3.32 (1H, br s, O*H*), 3.06 (1H, dq, J = 7.8, 6.9 Hz, C(=O)C*H*(CH$_3$)CH(OTES)), 2.63 (1H, qd, J = 7.2, 1.8 Hz, CH(OH)C*H*(CH$_3$)C(=O)), 1.63−1.43 (6H, m, CH_3CH_2, CH(OTBS)C*H*(CH$_3$), CH(OTES)C*H*(CH$_3$), CH_2CH_3), 1.15 (3H, d, J = 7.5 Hz, CH(OH)CH(C*H*$_3$)C(=O)), 0.98−0.83 (12H, m, C*H*$_3$CH$_2$, CH_2CH_3, C(=O)CH(C*H*$_3$)CH(OTES), CH(OTES)CH-(C*H*$_3$)CH$_2$), 0.93 (9H, t, J = 7.5 Hz, Si(CH$_2$C*H*$_3$)$_3$), 0.88 (9H, s, SiC(C*H*$_3$)$_3$), 0.72 (3H, d, J = 6.6 Hz, CH(OTBS)CH(C*H*$_3$)CH(OH)), 0.55 (6H, q, J = 7.5 Hz, Si(C*H*$_2$CH$_3$)$_3$), 0.09 (3H, s, Si(C*H*$_3$)$_A$-(CH$_3$)$_B$), 0.07 (3H, s, Si(CH$_3$)$_A$(C*H*$_3$)$_B$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 219.1, 79.1, 73.0, 70.6, 48.6, 47.3, 39.3, 38.0, 27.4, 25.9, 24.4, 18.1, 15.4, 14.0, 12.5, 10.6, 9.0, 8.0, 7.0, 5.3, −4.4, −4.5; IR (film, cm^{-1}) 3533, 2961, 2938, 2880, 2859, 1699, 1463, 1381, 1251, 1150, 1130, 1107, 1059, 1006, 973, 871, 835, 775, 739, 729, 666; $[\alpha]^{20}_D$ +52.1 (*c* 0.9, $CHCl_3$). **35b**: Not characterized because a small amount was isolated. **35c**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.95 (1H, apt t, J = 5.4 Hz, C*H*(OH)), 3.93 (1H, dd, J = 6.0, 2.7 Hz, C*H*(OTES)), 3.71 (1H, ddd, J = 8.4, 6.0, 2.4 Hz, C*H*(OTBS)), 2.96 (1H, dq, J = 8.4, 7.5 Hz, C(=O)C*H*(CH$_3$)CH(OTES)), 2.86 (1H, qd, J = 7.2, 6.0 Hz, CH(OH)C*H*(CH$_3$)C(=O)), 1.65−1.46 (5H, m, $CH_3CH_AH_B$ or $CH_AH_BCH_3$, CH_3CH_2 or CH_2CH_3, CH(OTBS)C*H*(CH$_3$), CH(OTES)C*H*(CH$_3$)), 1.22−1.12 (1H, m, $CH_3CH_AH_B$ or $CH_AH_BCH_3$), 1.16 (3H, d, J = 7.2 Hz, CH(OH)-CH(C*H*$_3$)C(=O)), 0.97−0.78 (15H, m, CH(OTBS)CH(C*H*$_3$), C(=O)CH(C*H*$_3$), CH(OTES)CH(C*H*$_3$), CH_3CH_2, CH_2CH_3), 0.94 (9H, t, J = 8.1 Hz, Si(CH$_2$C*H*$_3$)$_3$), 0.90 (9H, s, SiC(C*H*$_3$)$_3$), 0.59 (6H, q, J = 8.1 Hz, Si(C*H*$_2$CH$_3$)$_3$), 0.11 (3H, s, Si(C*H*$_3$)$_A$(CH$_3$)$_B$), 0.09 (3H, s, Si(CH$_3$)$_A$(C*H*$_3$)$_B$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 216.6, 77.54, 77.51, 74.1, 49.2, 48.9, 39.1, 37.5, 27.4, 25.9, 24.3, 18.0, 15.7, 13.7, 12.6, 11.0, 10.2, 7.4, 7.0, 5.3, −3.7, −4.4; IR (film, cm^{-1}) 3524, 2961, 2938, 2879, 2861, 1712, 1463, 1415, 1380, 1361, 1255, 1132, 1113, 1056, 1006, 977, 872, 835, 814, 774, 738, 667; $[\alpha]^{20}_D$ −2.47 (*c* 2.0, $CHCl_3$).

(3*R*,4*S*,8*S*,9*S*,10*S*)-3-*tert*-Butyldimethylsilyloxy-4,6,8,10-tetramethyl-9-triethylsilyloxydodecane-5,7-dione (36). Oxalyl chloride (152 μL, 0.305 mmol) was added dropwise to a solution of DMSO (43 μL, 0.609 mmol) in CH_2Cl_2 (870 μL) at −78 °C, and the solution was stirred for 30 min. Alcohol **35** (108 mgs, 0.209 mmol) was added via a cannula, and the resulting solution was stirred for 45 min at −78 °C. Et_3N (170 μL, 0.122 mmol) was then added dropwise over several minutes and stirred at −78 °C for 30 min before warming to 0 °C and stirring for 1 h. The reaction was quenched by pouring onto $NaHSO_4$ (1 M, 10 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organics were concentrated in vacuo, taken up in Et_2O (50 mL), washed in $NaHSO_4$ (1 M, 10 mL), H_2O (10 mL), $NaHCO_3$ (sat aq., 10 mL), and brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. (Alternatively, the reaction was quenched by the addition of NH_4Cl (sat. aq, 20 mL), and the product was extracted with CH_2Cl_2 (3 × 20 mL)). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo and purified by column chromatography to give product **36** (85 mg, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) (predominantly keto form) δ 4.00 (1H, q, J = 7.2 Hz, C(=O)C*H*(CH$_3$)C(=O)), 3.86 (1H, apt q, J = 5.7 Hz, C*H*(OTBS)), 3.75 (1H, dd, J = 8.4, 2.4 Hz, C*H*(OTES)), 2.93 (1H, qd, J = 6.9. 6.0 Hz, CH(OTBS)C*H*(CH$_3$)), 2.83 (1H, dq, J = 8.7, 6.9 Hz, C(=O)C*H*(CH$_3$)CH(OTES)), 1.67−1.12 (5H, m, CH_3CH_2, C*H*(CH$_3$)-CH_2CH_3, CH(CH$_3$)C*H*$_2$CH$_3$), 1.26 (3H, d, J = 7.2 Hz, C(=O)CH-(C*H*$_3$)C(=O)), 1.08 (3H, d, J = 6.9 Hz, CH(OTBS)CH(C*H*$_3$)-C(=O)), 1.01 (3H, d, J = 6.9 Hz, C(=O)CH(C*H*$_3$)CH(OTES)), 0.95−0.86 (18H, m, Si(CH$_2$C*H*$_3$)$_3$), C*H*$_3$CH$_2$, CH_2CH_3, CH(OTES)-CH(C*H*$_3$)CH$_2$), 0.91 (9H, s, SiC(C*H*$_3$)$_3$), 0.53 (6H, q, J = 8.1 Hz, Si(C*H*$_2$CH$_3$)$_3$), 0.083 (3H, s, Si(C*H*$_3$)$_A$(CH$_3$)$_B$), 0.075 (3H, s, Si(CH$_3$)$_A$(C*H*$_3$)$_B$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 212.2, 210.2, 80.0, 74.5, 61.8, 49.7, 49.4, 40.1, 27.6, 25.9, 24.6, 18.2, 15.2, 14.2, 13.8, 12.6, 12.2, 9.4, 6.9, 5.2, −4.3, −4.4; IR (film, cm^{-1}) 2960, 2937, 2879, 2860, 1727, 1701, 1462, 1379, 1362, 1254, 1130, 1115, 1054, 1005, 873, 836, 793, 776, 738, 725, 673.

(2*S*,3*S*)-2,3-Dihydro-6-[1*S*,2*R*]-(2-*tert*butyldimethylsilyloxy-1-methylbutyl)-2-[1*S*]-(1-methylpropyl)-3,5-dimethyl-pyran-4-one (37). To a solution of dione **36** (88.6 mg, 0.172 mmol) in $CDCl_3$ (3 mL) was added trifluoroacetic acid (5 drops) at room temperature with stirring. The solution was stirred for approximately 1 h or until TLC analysis showed the consumption of starting material. The solution was diluted with Et_2O (50 mL), washed with $NaHCO_3$ (sat. aq, 30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The product was purified by column chromatography (100% CH_2Cl_2, R_f = 0.31), yielding 41.7 mg (63%) of compound **37** as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81 (1H, dt, J = 9.0, 4.2 Hz, C*H*(OTBS)), 3.71 (1H, dd, J = 12.3, 3.3 Hz, CH(CH$_3$)C*H*(O)CH(CH$_3$)), 2.81 (1H, dq, J = 9.0, 7.2 Hz, CH(OTBS)C*H*(CH$_3$)), 2.46 (1H, dq J = 12.3, 6.9 Hz, C(=O)C*H*(CH$_3$)CH(O)), 1.74 (3H, s, C(O)=C(C*H*$_3$)C(=O)), 1.80−1.66 (1H, m, CH(O)C*H*(CH$_3$)CH$_2$), 1.62−1.44 (2H, m, $CH_3CH_AH_BCH$(OTBS), CH(CH$_3$)C*H*$_A$H$_B$CH$_3$), 1.41−1.19 (2H, m, $CH_3CH_AH_BCH$(OTBS), CH(CH$_3$)CH$_A$*H*$_B$CH$_3$), 1.14 (3H, d, J = 7.2 Hz, CH(OTBS)CH(C*H*$_3$)), 1.06 (3H, d, J = 6.9 Hz, C(=O)-CH(C*H*$_3$)CH(O)), 1.02 (3H, d, J = 6.9 Hz, CH(O)CH(C*H*$_3$)CH$_2$), 0.94 (3H, t, J = 7.5 Hz, CH(CH$_3$)CH$_2$C*H*$_3$), 0.90 (9H, s, SiC(C*H*$_3$)$_3$), 0.84 (3H, t, J = 7.2 Hz, C*H*$_3$CH$_2$), 0.07 (3H, s, Si(C*H*$_3$)$_A$(CH$_3$)$_B$), 0.06 (3H, s, Si(CH$_3$)$_A$(C*H*$_3$)$_B$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 195.9, 173.4, 108.6, 86.6, 74.5, 41.2, 40.5, 35.2, 27.8, 25.9, 22.0, 18.2, 16.1 (2), 11.8, 10.6, 9.4, 8.0, −4.2, −4.5; IR (film, cm^{-1}) 2962, 2933, 2881, 2859, 1668, 1618, 1472, 1462, 1376, 1359, 1354, 1254, 1191, 1157, 1144, 1106, 1073, 1054, 1035, 1005, 879, 856, 836, 794, 775, 675; $[\alpha]^{20}_D$ −99.8 (*c* 0.4, $CHCl_3$).

(2*S*,3*S*)-2,3-Dihydro-6-[(1′*S*,2′*R*)-2-hydroxy-1-methylbutyl]-3,5-dimethyl-2-[(1″*S*)-1-methylpropyl]-4H-pyran-4-one (3). A solution of silyl ether **36** (41.7 mg, 0.109 mmol) in HF/pyr/pyr (750 μL; from a stock solution containing dry THF (10 mL), pyridine (5 mL), and pyridinium hydrofluoride (2.1 g)) and H_2O (80 μL) was stirred at room temperature in a Teflon-screw-cap jar for 12 days or until TLC indicated the consumption of starting material. The solution was diluted with Et_2O (30 mL), washed with $CuSO_4$ (sat. aq, 15 mL), $NaHCO_3$ (sat. aq, 15 mL), and brine (15 mL), dried ($MgSO_4$), and concentrated in vacuo. The product was purified by column chromatography (10% Et_2O/CH_2Cl_2, R_f = 0.33), yielding 26.4 mg (90%) of product **3** as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (1H, dd, J = 12.3, 3.3 Hz, C*H*(O)-CH(CH$_3$)CH$_2$CH$_3$), 3.65 (1H, ddd, J = 8.4, 6.6, 3.9 Hz, C*H*(OH)), 2.77 (1H, apt qn, J = 7.2 Hz, CH(OH)C*H*(CH$_3$)), 2.49 (1H, dq, J = 12.3, 6.6 Hz, C(=O)C*H*(CH$_3$)), 1.88 (1H, br s, O*H*), 1.73 (3H, s, C(O)=C(C*H*$_3$)C(=O)), 1.76−1.70 (1H, m, CH(O)C*H*(CH$_3$)-CH_2CH_3), 1.60−1.53 (1H, m, CH(CH$_3$)C*H*$_A$H$_B$CH$_3$), 1.52−1.45

(1H, m, $CH_3CH_AH_BCH(OH)$), 1.43−1.35 (1H, m, $CH_3H_AH_BCH(OH)$), 1.28−1.22 (1H, m, $CH(CH_3)CH_AH_BCH_3$)), 1.20 (3H, d, J = 7.2 Hz, $CH(OH)CH(CH_3)$), 1.08 (3H, d, J = 6.6 Hz, $C(=O)CH(CH_3)$), 1.03 (3H, d, J = 6.6 Hz, $CH(CH_3)CH_2CH_3$), 0.96 (3H, t, J = 7.2 Hz, $CH_3CH_2CH(OH)$, 0.94 (3H, d, J = 7.2 Hz, $CH(CH_3)CH_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 195.7, 173.0, 108.6, 87.0, 75.1, 41.6, 40.6, 35.1, 28.0, 22.0, 16.2, 13.2, 11.7, 10.6, 10.2, 9.3. ^{1}H and ^{13}C NMR (600 MHz, $CDCl_3$) reported in Table 1. IR (film, cm^{-1}) 3435, 2967, 2935, 2878, 1664, 1650, 1609, 1459, 1378, 1357, 1196, 1144, 1070, 1029, 977; $[\alpha]^{20}_D$ −137.5 (*c* 0.9, $CHCl_3$), UV ($CHCl_3$) 275 nm (ϵ 20 100).

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Supporting Information Available: General experimental details, detailed experimental procedures, spectroscopic data for compounds **1**, **2**, **4**−**8**, **16**, **17**, **19**, **21**, and **26**−**30**, and copies of ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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