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Stereocontrolled Synthesis of 1,3-Diols from Enones: Cooperative Lewis Base-Mediated Intramolecular Carbonyl Hydrosilylations

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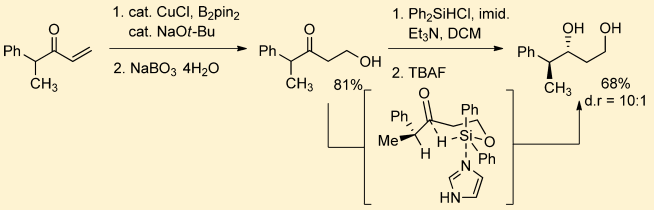
Supporting Information

ABSTRACT: A streamlined synthesis of β-hydroxy ketone substrates has been developed to further investigate a recently discovered cooperative Lewis base-mediated intramolecular carbonyl hydrosilylation reaction. The synthesis features an enone β-borylation/oxidation sequence that has proven to be quite general and high-yielding. This has allowed for additional investigations into the diastereoselectivity of the hydrosilylation reaction through the preparation of important polyketide fragments.

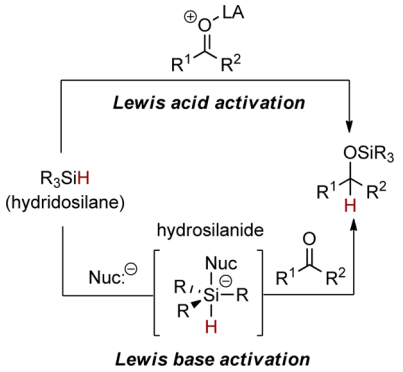


INTRODUCTION

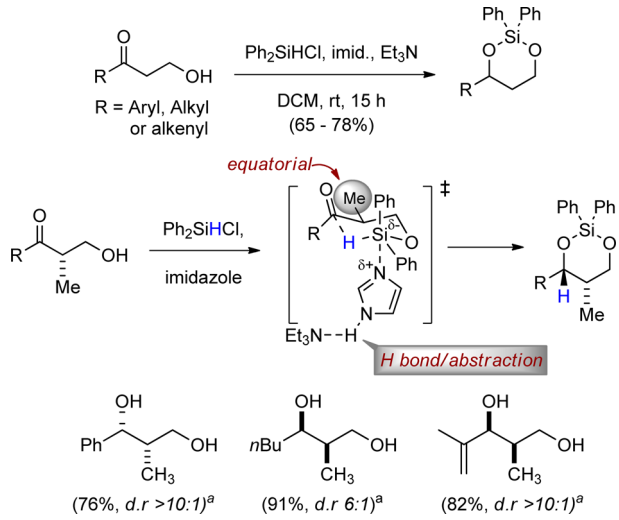
Hydridosilanes, or organosilicon compounds containing at least one Si−H group, have the ability to serve as a formal hydride source in part because this bond is polarized as $Si^{\delta+}-H^{\delta-}$. A range of reductions involving hydridosilanes are known, and there are several excellent reviews dedicated to reactions of organosilicon hydrides.[1−4] One of the earliest reports by Anderson 55 years ago described spontaneous reactions of triethylsilane with inorganic halides and acids to generate the corresponding free metals and hydrogen gas, respectively.[5] Reductions of carbonyls by hydridosilanes, however, most often require an activation event.[1] This can be either Lewis acid activation of the carbonyl compound to increase its electrophilicity or nucleophilic activation at the silicon center to create a valence-expanded pentacoordinate hydrosilanide (Scheme 1).[6]

Our group recently reported a new twist on this well-known reaction with the discovery of a novel intramolecular carbonyl hydrosilylation process.[7] β-Hydroxy ketones can be converted directly to cyclic siloxane products by the action of diphenylchlorosilane, imidazole, and triethylamine (Scheme 2). The proposed mechanism is as illustrated with nucleophilic activation at silicon by imidazole to generate a transient hydrosilanide.[8,9] The developing negative charge on silicon can be stabilized by each phenyl substituent and the positively charged imidazolium by hydrogen bonding/abstraction with triethylamine.[10,11] Hydride is then delivered from silicon via a six-membered chairlike transition state, which leads to useful

Scheme 1. Activation Modes for Carbonyl Hydrosilylation



Scheme 2. Cooperative Lewis Base-Mediated Intramolecular Hydrosilylations[a]



[a]Isolated yields after desilylation with TBAF. Ratios were determined by ^{1}H NMR spectroscopy.

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diastereoselectivities.[12] For instance, placement of a methyl substituent between the hydroxyl group and the ketone forces this group into a preferred equatorial position, thus directing the face of the carbonyl to which the hydride is then added, leading in each case to the *syn*-propionate product.

Herein we describe an optimization of this reaction as a general method for the direct conversion of β-hydroxy ketones to cyclic siloxanes. An efficient enone β-borylation/oxidation sequence was employed to synthesize the β-hydroxy ketone substrates, which allowed for further investigations into the diastereoselectivity of the hydrosilylation reaction. The utility of the hydrosilylation reaction was then highlighted through the preparation of several important polyketide fragments.

RESULTS AND DISCUSSION

β-Hydroxy ketone substrates for our previous work were typically prepared according to the method of Martin et al.[13] via a five-step sequence from various commercial aldehydes as outlined in Scheme 3, with overall yields of 30−40%. As an alternative, we envisioned a shorter and more versatile β-borylation/oxidation sequence from readily available terminal enones.

Many reagents have been described to promote the conjugate or 1,4-addition of a boronate ester from a diboron reagent.[14] Careful analysis of these methods, however, revealed only a select number of examples involving terminal α,β-unsaturated ketones (enones).[15] This is likely a reflection of the challenge associated with terminal enone transformations due to their decreased stability relative to their ester- or di-substituted counterparts.[16] For instance, while Bonet et al.[17] reported the successful β-borylation of a variety of conjugated esters using Ph_3P and $CsCO_3$, we found that this system resulted in rapid decomposition of terminal enones. Chea et al.[18] included methyl vinyl ketone as a single terminal enone substrate in their report on the scope of a copper-catalyzed β-borylation. When we applied these conditions to phenyl vinyl ketone using the prescribed 1:1.1 stoichiometric ratio of enone to bis(pinacolato)diboron (B_2pin_2), the boronate ester product **1** was obtained in only 38% yield (Table 1, entry 1). It was suspected that the inherent instability of terminal enones was in part responsible for the low yield. When the reaction was instead performed using a 1:0.8 enone:diboron molar ratio, the yield of **1** was 64% (51% based on enone; entry 2). Increasing the equivalents to 2:1 in favor of the enone further improved the yield to 82% (entry 3). Importantly, no starting phenyl vinyl ketone was recovered from this mixture, supportive of a competing decomposition during the course of the reaction for these particular substrates. The terminal enones for entries 4, 5, and 6 proved similarly sensitive and were thus used in slight excess (1.2 equiv) to obtain good yields of the corresponding boronate ester products **2**, **3**, and **4** without sacrificing a large excess of the enone.

Interestingly, when the reaction was performed using PMB-protected Roche ester-derived enone **5** with a 1:1.1 enone:diboron ratio (Table 2, entry 1), the product was obtained in 91% yield. Along with the corresponding boronate ester **9**, a small amount of starting enone was observed, indicating an increased stability for this particular substrate. TBS-protected Roche ester enone **6**

Scheme 3. Previous β-Hydroxy Ketone Synthesis and Potential β-Borylation/Oxidation Alternative

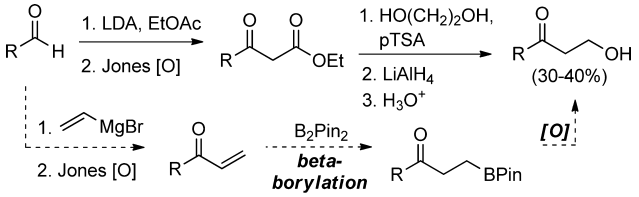
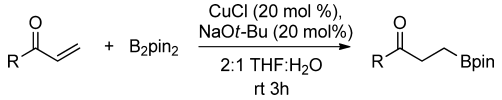
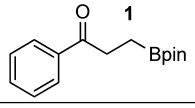
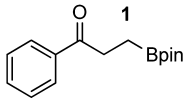
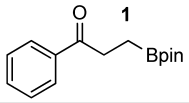
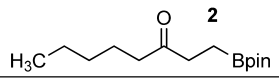
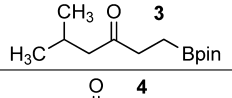
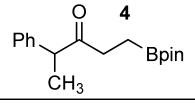


Table 1. Optimization of a Copper-Catalyzed Terminal Enone β-Borylation



Entry	Product	Equiv. B_2pin_2	Yield
1		1.1	38[a]
2		0.8	64[b]
3		0.5	82[b]
4		0.8	64[b]
5		0.8	79[b]
6		0.8	68[b]

[a]Yield based on enone starting material. [b]Yield based on bis(pinacolato)diboron.

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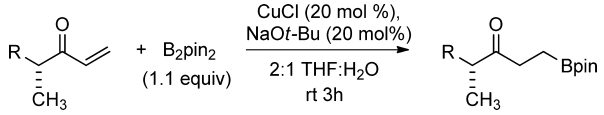
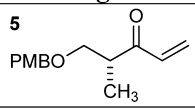
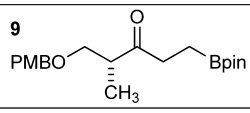
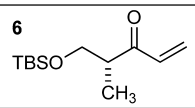
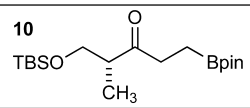
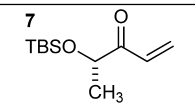
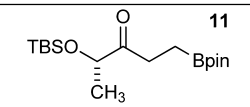
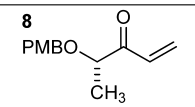
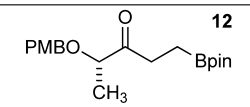
Table 2. β-Borylation of Chiral Enone Substrates Using Excess Diboron

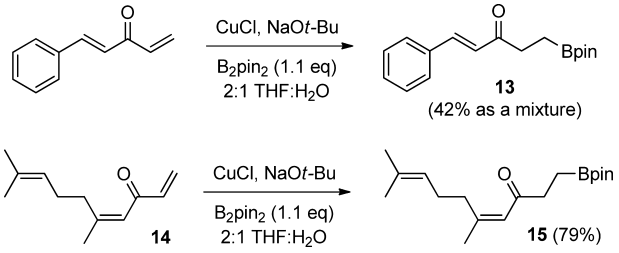


Entry	Starting enone	Product	Yield
1	**5** 	**9** 	91
2	**6** 	**10** 	94
3	**7** 	**11** 	82
4	**8** 	**12** 	89

and lactate-derived substrates **7**[19] and **8** (entries 2–4) proved similarly robust, allowing for the chiral enone and arguably more precious substrates to serve as the limiting reactants and giving the corresponding ketoboronate esters **10**, **11**, and **12** in high yield.

The chemoselectivity of the β-borylation reaction was also explored (Scheme 4). β-Borylation of a cinnamaldehyde-derived

Scheme 4. Chemoselective Enone β-Borylation

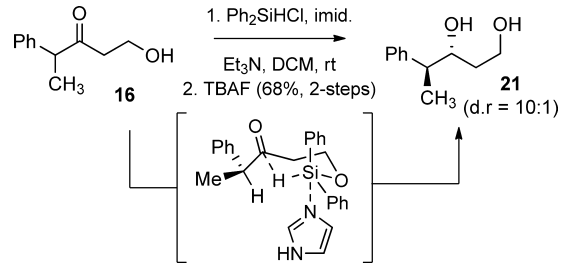


dienone[20] proved only moderately selective, giving boronate ester **13** in 42% yield as a mixture along with what have been tentatively assigned as internally borylated and bis-β-borylated adducts. The trisubstituted conjugated alkene of nerol-derived dienone **14**, however, was unaffected by the reaction conditions, providing the corresponding boronate ester **15** in 79% isolated yield with complete chemoselectivity.

Completion of the synthesis by oxidative cleavage of the boronate ester was best accomplished using sodium perborate (Scheme 5).[21] Yields ranged from good to quantitative. The sequence could also be performed without isolation and purification of the intermediate boronate ester, taking the crude product from the copper-catalyzed β-borylation directly into the perborate oxidation. This resulted in an overall enhancement of the yield, presumably due to the decreased handling of the intermediate boronate esters, which are susceptible to hydrolysis.[22]

Convenient access to β-hydroxy ketone substrates **16**–**20** allowed for further explorations of the diastereoselectivity of the intramolecular hydrosilylation reaction complementary to those previously reported (Scheme 2).[7] For instance, treatment of **16** with our optimized hydrosilylation conditions followed by desilylation with TBAF gave diol **21** in 68% yield as a 10:1 mixture of diastereomers, as determined by ^{1}H NMR spectroscopy (Scheme 6). Comparison to literature data allowed

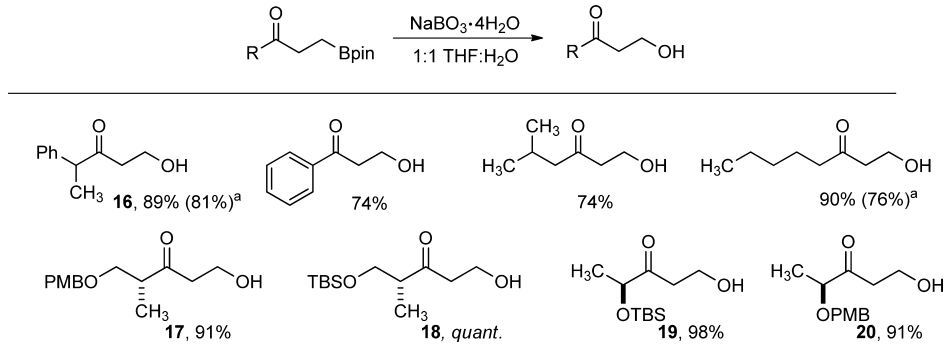
Scheme 6. Felkin-Controlled Intramolecular Hydrosilylation



for assignment of the major stereoisomer as the *anti*-propionate product.[23] This can be rationalized as a Felkin-controlled addition,[24] in which the phenyl group as the largest substituent is projected away from the incoming nucleophilic hydride.

Results from additional hydrosilylations of substrates containing α'-stereocenters are outlined in Scheme 7. The TBS-protected lactate derivative **19** proved unreactive, consistent with previous observations when using sterically demanding compounds.[7] Switching to the smaller PMB-protected lactate-derived substrate **20** then allowed the reaction to proceed to **22**, albeit with no selectivity. Neither the PMB- nor TBS-Roche ester-derived substrate **17** or **18**, respectively, reacted with an appreciable level of selectivity. The major stereoisomer in each

Scheme 5. Boronate Ester Oxidation[a]



[a]Yields in parentheses are from the starting enone without isolation/purification of the boronate ester intermediate.

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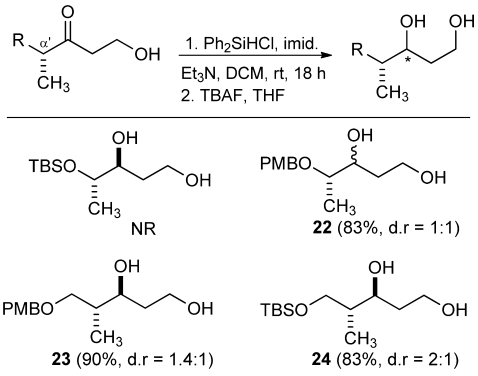
Scheme 7. Effect of α′-Stereocenters on the Intramolecular Carbonyl Hydrosilylation

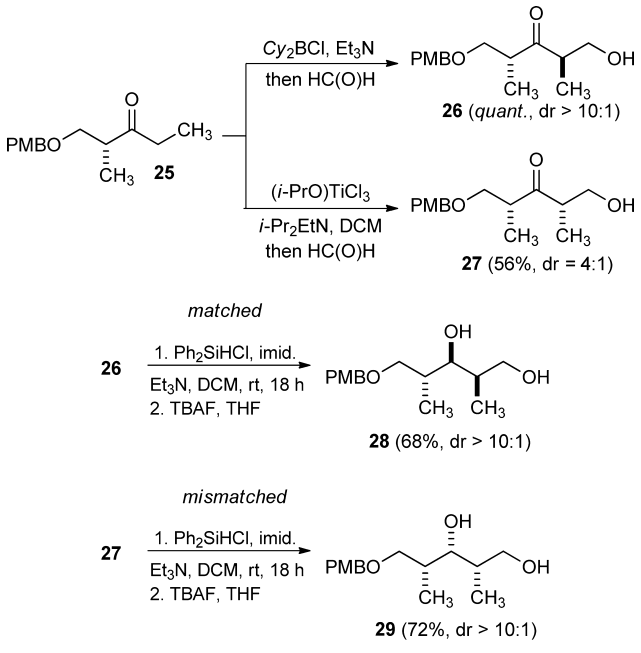


case was the *anti*-propionate product (**23**[25] or **24**,[26] respectively), consistent with a Felkin-control model.

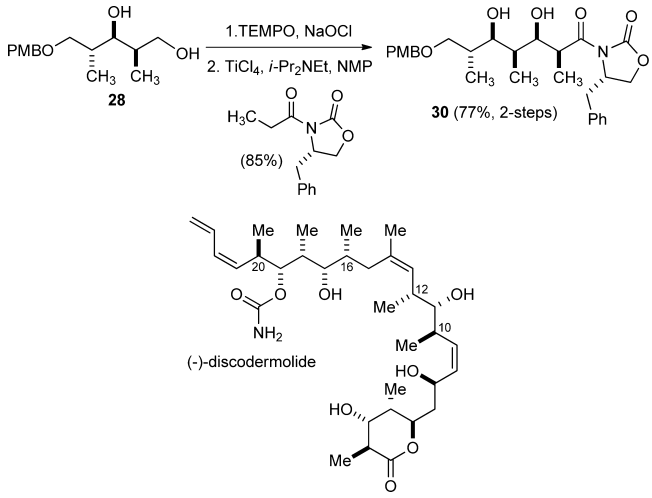
The nominal influence of the α′-stereocenter on the stereoselectivities in Scheme 7 suggested that both *syn,syn*- and *anti,syn*-stereotriads could be prepared by intramolecular hydrosilylation with high levels of stereocontrol. To that end, enolization of ethyl ketone **25**[27] with chlorodicyclohexylborane and triethylamine or trichlorotitanium isopropoxide and Hünig's base followed by reaction with formaldehyde gave hydroxy ketone **26** or **27**, respectively, as previously described (Scheme 8).[28,29] Intramolecular hydrosilylation of the matched substrate **26** gave the expected *anti,syn*-stereotriad **28** in 68% yield as a single diastereomer, as determined by ^{1}H NMR spectroscopy.[30] Importantly, hydrosilylation of **27** proceeded with similarly high levels of selectivity, with the methyl group within the six-membered cyclic transition state proving to be the dominant stereocontrolling element, affording the *syn,syn*-stereotriad **29** in 72% yield (dr >10:1).[31]

Stereotriads themselves are common to a number of important natural products and can serve as a starting point from which to build up extended polypropionate systems. For instance, compound **28** maps onto the C_{10}−C_{12} region of (−)-discodermolide, and a similar substrate served as a key intermediate for multiple fragment syntheses in the preparation of this compound by the Smith group.[32] As a demonstration, the primary alcohol of **28** was oxidized with TEMPO, and the resulting aldehyde underwent an Evans *syn*-aldol reaction[33] to generate **30** containing the C_{16}−C_{20} stereopentad of discodermolide (Scheme 9).

Scheme 8. Stereotriad Synthesis by Diastereoselective Intramolecular Hydrosilylation



Scheme 9. Synthesis of the C_{16}−C_{20} Stereopentad of (−)-Discodermolide from Hydrosilylation Adduct 30



CONCLUSION

In summary, a novel intramolecular carbonyl hydrosilylation protocol promoted by the combined action of imidazole and triethylamine bases has been developed. The reaction proceeds via a six-membered chairlike transition state, leading to useful and predictable diastereoselectivities. Access to β-hydroxy ketone substrates was streamlined through the use of a terminal enone β-borylation/oxidation sequence. This then allowed for further investigations into the stereoselectivity of the hydrosilylation reaction. Ultimately these results revealed the versatility of the protocol, which has the ability to generate both *syn,syn*- and *syn,anti*-stereotriads in high yield with similar stereocontrol. Products of this type represent important building blocks with which to prepare more complex polyketide targets, including discodermolide.

EXPERIMENTAL SECTION

General Procedure for β-Borylation of Terminal Enones (Compounds 1−4, 9−12, and 15). To a solution of copper(I) chloride (20 mol %) in THF (2 mL) was added NaO^{t}Bu (20 mol %), and the mixture was allowed to stir at room temperature for 10 min. Bis(pinacoloto)diboron (0.5−1.1 equiv; see Tables 1 and 2) was then added, and the resulting black solution was stirred for 10 min before addition of the appropriate enone and H_2O (1 mL), after which the mixture was stirred for 3 h. The reaction was then quenched with saturated aq. NaCl (10 mL), and the mixture was extracted with ethyl acetate (2 × 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica (10:1 hexanes/ethyl acetate).

1-Phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-one (1). (0.166 g, 64%). IR (neat): 2977, 2933, 1685, 1379, 1371,

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1316, 1221, 1144, 690 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, J = 7.0 Hz, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 3.16 (t, J = 7.0 Hz, 2H), 1.25 (s, 12H), 1.07 (t, J = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.8, 137.1, 133.0, 128.7, 128.2, 83.3, 33.9, 25.0.[34] ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.6. HRMS (TOF ESI+) calcd for $[C_{15}H_{21}BO_3 + Na]^+$ 283.1484, found 283.1490.

*1-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)octan-3-one (**2**).* (0.163 g, 64%). IR (neat): 2931, 1712, 1378, 1313, 1145, 968, 841 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 2.55 (t, J = 7.0 Hz, 2H), 2.37 (t, J = 7.5 Hz, 2H), 1.56 (quin, J = 7.5 Hz, 2H), 1.33−1.23 (m, 4H), 1.23 (s, 12H), 0.90 (t, J = 7.0 Hz, 2H), 0.87 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.0, 83.3, 42.4, 37.7, 31.6, 25.0, 24.0, 22.7, 14.1. ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.4. HRMS (TOF ESI+) calcd for $[C_{14}H_{27}BO_3 + Na]^+$ 277.1954, found 277.1943.

*5-Methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-one (**3**).* (0.284 g, 79%). IR (neat): 2957, 1711, 1414, 1379, 1370, 1313, 1144, 968, 872, 844 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 2.54 (t, J = 7.0 Hz, 2H), 2.26 (d, J = 6.5 Hz, 2H), 2.12 (m, 1H), 1.23 (s, 12H), 0.90 (d, J = 6.5 Hz, 6H), 0.88 (t, J = 6.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.5, 83.2, 51.5, 38.4, 25.2, 25.0, 22.8. ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.4. HRMS (TOF ESI+) calcd for $[C_{13}H_{25}BO_3 + Na]^+$ 263.1797, found 263.1791.

*4-Phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-one (**4**).* (0.197 g, 68%). IR (neat): 2976, 2930, 1712, 1371, 1315, 1144, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.31 (t, J = 7.5 Hz, 2H), 7.25−7.2 (m, 3H), 3.77 (q, J = 7.0 Hz, 1H), 2.52 (m, 2H), 1.38 (d, J = 7.0 Hz, 3H), 1.21 (s, 12H), 0.85 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.6, 141.2, 129.0, 128.1, 127.1, 83.2, 52.5, 36.3, 25.0, 17.9. ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.3. HRMS (TOF ESI+) calcd for $[C_{17}H_{25}BO_3 + Na]^+$ 311.1798, found 311.1799.

*(R)-5-((4-Methoxybenzyl)oxy)-4-methylpent-1-en-3-one (**5**).* To a solution of (*R*)-*N*-methoxy-3-((4-methoxybenzyl)oxy)-*N*,2-dimethylpropanamide[35] (0.649 g, 2.43 mmol, 1 equiv) in THF (13 mL) at −15 °C was added a freshly made solution of vinylmagnesium bromide (8.2 mL, 1.0 M, 3.2 equiv), and the mixture was stirred and allowed to warm to room temperature over 5 h. The reaction was quenched with aq. NH_4Cl, and the mixture was extracted with MTBE (3 × 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica (4:1 hexanes/EtOAc) provided compound **5** as a clear colorless oil (0.350 g, 62%). $[\alpha]_D^{20}$ = −9.3 (*c* 1.0, CH_2Cl_2). IR (neat): 2935, 2857, 1697, 1676, 1611, 1512, 1245, 1093, 1033, 972, 818 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 6.44 (dd, J = 11.0, 18.0 Hz, 1H), 6.28 (dd, J = 1.5, 18.0 Hz, 1H), 5.80 (dd, J = 1.5, 10.5 Hz, 1H), 4.44 (d, J = 11.0 Hz, 1H), 4.40 (d, J = 11.5 Hz, 1H), 3.80 (s, 3H), 3.67 (dd, J = 9.5, 2.0 Hz, 1H), 3.44 (dd, J = 8.5, 3.0 Hz, 1H), 3.17 (sextet, J = 6.0 Hz, 1H), 1.11 (d, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.7, 159.4, 135.7, 130.4, 129.4, 128.6, 113.9, 73.1, 71.9, 55.5, 43.9, 14.1. HRMS (TOF ESI+) calcd for $[C_{14}H_{18}O_3 + Na]^+$ 257.1154, found 257.1152.

*(R)-5-((tert-Butyldimethylsilyl)oxy)-4-methylpent-1-en-3-one (**6**).* To a solution of (*R*)-3-((*tert*-butyldimethylsilyl)oxy)-*N*-methoxy-*N*,2-dimethylpropanamide[36] (0.965 g, 3.74 mmol, 1 equiv) in THF (19 mL) at −15 °C was added a freshly made solution of vinylmagnesium bromide (12.0 mL, 1.0 M, 3.2 equiv), and the mixture was stirred and allowed to warm to room temperature over 5 h. The reaction was quenched with aq. NH_4Cl, and the mixture was extracted with MTBE (3 × 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica (10:1 hexanes/EtOAc) provided compound **6** as a clear colorless oil (0.455 g, 53%). $[\alpha]_D^{20}$ = −36.2 (*c* 1.0, CH_2Cl_2). IR (neat): 2956, 2929, 2857, 1700, 1680, 1463, 1252, 1099, 834, 775 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.45 (dd, J = 10.0, 17.5 Hz, 1H), 6.26 (dd, J = 1.5, 17.5 Hz, 1H), 5.79 (dd, J = 1.5, 10.5 Hz, 1H), 3.80 (dd, J = 7.5, 10.0 Hz, 1H), 3.62 (dd, J = 6.0, 9.5 Hz, 1H), 3.09 (sextet, J = 6.5 Hz, 1H), 1.07 (d, J = 7.0 Hz, 3H), 0.85 (s, 9H), 0.3 (s, 3H), 0.1 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.5, 136.3, 128.3, 65.6, 46.0, 26.0, 18.4, 13.6, −5.3. HRMS (TOF ESI+) calcd for $[C_{12}H_{24}O_2Si + Na]^+$ 251.1443, found 251.1443.

*(S)-4-((tert-Butyldimethylsilyl)oxy)pent-1-en-3-one (**7**).* To a solution of (*S*)-2-((*tert*-butyldimethylsilyl)oxy)-*N*-methoxy-*N*-methylpropanamide[37] (1.50 g, 2.07 mmol, 1 equiv) in THF (50 mL) at 0 °C was added a freshly made solution of vinylmagnesium bromide (8.0 mL, 1.5 M, 2.0 equiv), and the mixture was stirred for 1 h. The reaction was quenched with aq. NH_4Cl, and the mixture was extracted with MTBE (3 × 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica (10:1 hexanes/EtOAc) provided compound **7** as a clear colorless oil (0.812 g, 66%). $[\alpha]_D^{20}$ = −1.48 (*c* = 1.2, CH_2Cl_2). IR (neat): 2956, 2930, 2887, 2858, 1703, 1612, 1473, 1402, 1253, 1118, 1091, 935, 831, 814, 777 cm^{-1}. The NMR spectral data matched those previously reported in the literature:[19] ^1H NMR (500 MHz, $CDCl_3$): δ 6.87 (dd, J = 11.0, 18.0 Hz, 1H), 6.40 (dd, J = 2.0, 17.5 Hz, 1H), 5.77 (dd, J = 2.0, 11.0 Hz, 1H), 4.29 (q, J = 6.5 Hz, 1H), 1.31 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.9, 130.6, 129.5, 74.3, 25.7, 20.9, 18.1, −4.8, −5.0.

*(S)-4-((4-Methoxybenzyl)oxy)pent-1-en-3-one (**8**).* To a solution of (*S*)-*N*-methoxy-2-((4-methoxybenzyl)oxy)-*N*-methylpropanamide[38] (0.585 g, 2.31 mmol, 1 equiv) in THF (50 mL) at −15 °C was added a freshly made solution of vinylmagnesium bromide (2.88 mL, 2.0 M, 2.5 equiv), and the mixture was stirred for 1 h. The reaction was quenched with aq. NH_4Cl, and the mixture was extracted with MTBE (3 × 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica (4:1 hexanes/EtOAc) provided compound **8** as a clear colorless oil (0.329 g, 65%). $[\alpha]_D^{20}$ = −18.4 (*c* 1.2, CH_2Cl_2). IR (neat): 2916, 2849, 1699, 1611, 1513, 1402, 1246, 1173, 1092, 1032, 988, 968, 820 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 6.79 (dd, J = 10.0, 17.0 Hz, 1H), 6.43 (dd, J = 2.0, 17.5 Hz, 1H), 5.80 (dd, J = 2.0, 11.0 Hz, 1H), 4.49 (d, J = 11.0 Hz, 1H), 4.38 (d, J = 11.0 Hz, 1H), 4.09 (q, J = 7.0 Hz, 1H), 3.81 (s, 3H), 1.36 (d, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.6, 159.4, 130.9, 129.8, 129.6, 129.5, 113.9, 79.5, 71.5, 55.3, 17.8. HRMS (TOF ESI+) calcd for $[C_{13}H_{16}O_3 + Na]^+$ 243.0997, found 243.1002.

*(R)-1-((4-Methoxybenzyl)oxy)-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-one (**9**).* Prepared according to the general procedure for β-borylation. (0.197 g, 91%). $[\alpha]_D^{20}$ = −20.3 (*c* = 1.2, CH_2Cl_2). IR (neat): 2976, 2933, 1711, 1612, 1513, 1371, 1245, 1144, 819 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 4.42 (d, J = 11.0 Hz, 1H), 4.38 (d, J = 11.0 Hz, 1H), 3.80 (s, 3H), 3.60 (dd, J = 8.0, 9.5 Hz, 1H), 3.40 (dd, J = 5.5, 9.0 Hz, 1H), 2.86 (m, 1H), 2.64 (dt, J = 1.5, 7.0 Hz, 2H), 1.22 (s, 12H), 1.06 (d, J = 6.5 Hz, 3H), 0.90 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.8, 159.3, 130.5, 129.4, 113.9, 83.2, 73.1, 72.3, 55.5, 46.2, 37.3, 31.8, 25.2, 25.0, 24.9, 13.9. ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.2. HRMS (TOF ESI+) calcd for $[C_{20}H_{31}BO_5 + Na]^+$ 385.2166, found 385.2156.

*(R)-1-((tert-Butyldimethylsilyl)oxy)-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-one (**10**).* Prepared according to the general procedure for β-borylation. (0.367 g, 94%). $[\alpha]_D^{20}$ = −21.1 (*c* 1.0, CH_2Cl_2). IR (neat): 2929, 2858, 1714, 1379, 1371, 1313, 1145, 1097, 835, 775 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.72 (dd, J = 10.0, 2.0 Hz, 1H), 3.56 (dd, J = 10.0, 4.0 Hz, 1H), 2.75 (m, 1H), 2.64 (t, J = 7.0 Hz, 2H), 1.23 (s, 6H), 1.22 (s, 6H), 1.02 (d, J = 6.5 Hz, 3H), 0.89 (m, 2H), 0.86 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 214.3, 83.2, 65.7, 48.5, 37.8, 26.0, 25.0, 24.9, 18.4, 13.4, −5.3. ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.7. HRMS (TOF ESI+) calcd for $[C_{18}H_{37}BO_4Si + Na]^+$ 379.2456, found 379.2461.

*(S)-4-((tert-Butyldimethylsilyl)oxy)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-one (**11**).* Prepared according to the general procedure for β-borylation. (0.270 g, 82%). $[\alpha]_D^{20}$ = −6.8 (*c* 1.1, CH_2Cl_2). IR (neat): 2955, 2931, 2858, 1716, 1379, 1371, 1314, 1251, 1145, 834, 776 cm^{-1}. ^{11}H NMR (500 MHz, $CDCl_3$): δ 4.15 (q, J = 6.5 Hz, 1H), 2.78 (ddd, J = 6.5, 6.5, 19.5 Hz, 1H), 2.69 (ddd, J = 7.0, 7.0, 19.5 Hz, 1H), 1.27 (d, J = 7.0 Hz, 3H), 1.22 (s, 6H), 1.22 (s, 6H), 0.91 (s, 9H), 0.88 (m, 2H), 0.7 (s, 3H), 0.6 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 215.1, 83.2, 74.9, 32.3, 26.0, 25.0, 24.9, 21.3,

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18.3, −4.5, −4.9. ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.4. HRMS (TOF ESI+) calcd for $[C_{17}H_{35}BO_4Si + Na]^+$ 365.2299, found 365.2307.

*(S)-4-((4-Methoxybenzyl)oxy)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-one (**12**).* Prepared according to the general procedure for β-borylation. (0.447 g, 89%). $[\alpha]_D^{20}$ = −6.2 (*c* 1.0, CH_2Cl_2). IR (neat): 2977, 2934, 1714, 1612, 1513, 1379, 1370, 1314, 1244, 1144, 1034, 822 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 4.51 (d, *J* = 11.0 Hz, 1H), 4.38 (d, *J* = 11.5 Hz, 1H), 3.93 (q, *J* = 7.0 Hz, 1H), 3.81 (s, 3H), 2.72 (t, *J* = 6.5 Hz, 2H), 1.32 (d, *J* = 7.0 Hz, 3H), 1.23 (s, 12H), 0.93 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.7, 159.2, 129.8, 129.5, 113.9, 83.1, 80.0, 71.4, 55.3, 32.4, 24.8, 24.8, 17.9. ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.6. HRMS (TOF ESI+) calcd for $[C_{19}H_{29}O_5B + Na]^+$ 371.2009, found 371.1998.

*(Z)-5,9-Dimethyldeca-1,4,8-trien-3-one (**14**).* To a solution of neral (0.3 g, 2.0 mmol, 1.0 equiv) in THF (5.5 mL) at 0 °C was added freshly prepared vinylmagnesium bromide (2.6 mL, 1.5 M, 4.0 mmol, 2.0 equiv), and the mixture was allowed to stir for 30 min. The reaction was quenched with saturated aq. NH_4Cl (25 mL), and the mixture was extracted with MTBE (3 × 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude allylic alcohol was redissolved in DCM (13 mL) and acetonitrile (1.3 mL) with 4 Å molecular sieves. *N*-Methylmorpholine-*N*-oxide (0.352 g, 3.0 mmol, 1.5 equiv) was added, and the mixture was stirred for 5 min before the addition of tetrapropylammonium perruthenate (0.070 g, 0.20 mmol, 0.1 equiv). The mixture was stirred for 15 h, filtered through a plug of silica with EtOAc, and concentrated in vacuo. Purification by flash chromatography on silica provided compound **14** as a clear pale-yellow oil (0.236 g, 66%). IR (neat): 2968, 2915, 2856, 1724, 1661, 1674, 1622, 1601, 1447, 1400, 1376, 1243, 1117, 983, 959, 853, 713 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.40 (dd, *J* = 9.5, 18.0 Hz, 1H), 6.25 (d, *J* = 1.5 Hz, 1H), 6.21 (dd, *J* = 1.0, 17.0 Hz, 1H), 5.73 (dd, *J* = 1.5, 11.0 Hz, 1H), 5.15 (tq, *J* = 1.5, 9.0 Hz, 1H), 2.61 (t, *J* = 7.5 Hz, 2H), 2.16 (q, *J* = 7.0 Hz, 2H), 1.93 (d, *J* = 1.5 Hz, 3H), 1.67 (d, *J* = 1.0 Hz, 3H), 1.63 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.1, 161.0, 138.3, 132.2, 127, 123.7, 122.3, 34.2, 26.8, 25.9, 25.7, 17.6. HRMS (TOF CI+) calcd for $[C_{12}H_{18}O + H]^+$ 179.1436, found 179.1430.

*(Z)-5,9-Dimethyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-deca-4,8-dien-3-one (**15**).* Prepared according to the general procedure for β-borylation. (0.048 g, 79%). IR (neat): 2975, 2927, 1687, 1620, 1443, 1414, 1371, 1310, 1243, 1145, 1093, 968, 842 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.03 (d, *J* = 1.5 Hz, 1H), 5.13 (tq, *J* = 1.5, 7.5 Hz, 1H), 2.57 (q, *J* = 7.0 Hz, 4H), 2.12 (q, *J* = 8.5 Hz, 2H), 1.85 (d, *J* = 1.5 Hz, 3H), 1.67 (d, *J* = 1.0 Hz, 3H), 1.61 (s, 3H), 1.24 (s, 12H), 0.90 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.6, 157.9, 131.9, 123.9, 123.6, 83.0, 39.0, 33.8, 26.8, 25.7, 25.6, 24.8, 17.7. HRMS (TOF ESI+) calcd for $[C_{18}H_{31}O_3B + Na]^+$ 329.2267, found 329.2256.

General C−B Oxidation Procedure (Compounds 16−20). To a solution of the boronate ester (1.0 equiv) in THF/H_2O (1:1, 0.1 M relative to boronate ester substrate) at room temperature open to air was added $NaBO_3{\cdot}4H_2O$ (5 equiv), and the mixture was stirred vigorously for 3 h. H_2O was then added (10 mL), and the reaction mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica (4:1 to 1:1 hexanes/ethyl acetate).

*1-Hydroxy-4-phenylpentan-3-one (**16**).* (0.097 g, 89%). The NMR spectral data matched those previously reported in the literature:[39] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (t, *J* = 7.0 Hz, 2H), 7.28 (d, *J* = 7.0 Hz, 1H), 7.21 (d, *J* = 7.0 Hz, 2H), 3.79−3.73 (m, 3H), 2.61 (t, *J* = 5.0 Hz, 2H), 1.41 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.8, 140.1, 129.1, 127.9, 127.4, 58.1, 53.4, 42.7, 17.1.

*(R)-5-Hydroxy-1-((4-methoxybenzyl)oxy)-2-methylpentan-3-one (**17**).* (0.098 g, 91%). $[\alpha]_D^{20}$ = −2.03 (*c* 1.1, CH_2Cl_2). IR (neat): 3430, 2937, 1707, 1612, 1512, 1459, 1364, 1302, 1245, 1173, 1076, 1032, 818 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.40 (d, *J* = 11.5 Hz, 1H), 3.90−3.80 (m, 2H), 3.80 (s, 3H), 3.59 (dd, *J* = 8.5, 9.5 Hz, 1H), 3.47 (dd, *J* = 7.0, 9.0 Hz, 1H), 2.89 (m, 1H), 2.76 (ddd, *J* = 4.0, 6.5, 17.5 Hz, 1H) 2.71 (ddd, *J* = 4.0, 6.0, 17.5 Hz, 1H), 2.56 (bt, *J* = 6.5 Hz, O−H), 1.07 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 214.4, 159.3, 129.8, 129.3, 113.8, 73.0, 71.9, 58.1, 55.3, 46.7, 44.0, 24.9, 13.2. HRMS (TOF ESI+) calcd for $[C_{14}H_{20}O_4 + Na]^+$ 275.1259, found 275.1251.

*(R)-1-((tert-Butyldimethylsilyl)oxy)-5-hydroxy-2-methylpentan-3-one (**18**).* (0.099 g, 100%). $[\alpha]_D^{20}$ = −34.5 (*c* 0.8, CH_2Cl_2). IR (neat): 3399, 2955, 2929, 2857, 1707, 1472, 1388, 1253, 1078, 834, 775 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.90−3.78 (m, 2H), 3.74 (dd, *J* = 7.5, 9.5 Hz, 1H), 3.66 (dd, *J* = 5.0, 9.5 Hz, 1H), 2.83−2.68 (m, 3H), 2.57 (t, *J* = 6.5 Hz, 1H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 215.2, 65.8, 58.3, 49.1, 44.6, 26.0, 18.4, 13.0, −5.4, −5.4. HRMS (TOF ESI+) calcd for $[C_{12}H_{26}O_3Si + Na]^+$ 269.1549, found 269.1549.

*(S)-4-((tert-Butyldimethylsilyl)oxy)-1-hydroxypentan-3-one (**19**).* (0.173 g, 98%). $[\alpha]_D^{20}$ = −3.6 (*c* 1.0, CH_2Cl_2). IR (neat): 3429, 1256, 2930, 2886, 2858, 1715, 1473, 1362, 1252, 1118, 832, 776 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.15 (q, *J* = 7.0 Hz, 1H), 3.86 (s, 2H), 2.90 (ddd, *J* = 5.0, 6.0, 19.0 Hz, 1H), 2.79 (ddd, *J* = 5.0, 5.0, 18.5 Hz, 1H), 2.42 (bs, O−H), 1.29 (d, *J* = 7.0 Hz, 3H), 0.92 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 215.5, 75.0, 57.9, 39.4, 25.9, 20.9, 18.2, −4.5, −4.9. HRMS (TOF ESI+) calcd for $[C_{11}H_{24}O_3Si + Na]^+$ 255.1392, found 255.1386.

*(S)-1-Hydroxy-4-((4-methoxybenzyl)oxy)pentan-3-one (**20**).* (0.271 g, 91%). $[\alpha]_D^{20}$ = −30.7 (*c* 0.8, CH_2Cl_2). IR (neat): 3429, 2937, 1713, 1612, 1513, 1245, 1091, 1030, 818 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 4.48 (s, 2H), 3.92 (q, *J* = 7.0 Hz, 1H), 3.86 (t, *J* = 5.5 Hz, 2H), 3.81 (s, 3H), 2.83 (ddd, *J* = 5.5, 5.5, 18.0 Hz, 1H), 2.78 (ddd, *J* = 4.5, 5.5, 18.5 Hz, 1H), 1.33 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 214.0, 159.5, 129.5, 129.4, 113.9, 80.2, 71.6, 57.7, 55.3, 39.5, 17.2. HRMS (TOF CI+) calcd for $[C_{13}H_{18}O_4 + NH_4]^+$ 256.1549, found 256.1540.

General Intramolecular Hydrosilylation Procedure (Compounds 21−24, 28, and 29). To a solution of the β-hydroxy ketone (1 equiv) in DCM (0.1 M relative to the hydroxy ketone substrate) at 0 °C were added triethylamine (6.0 equiv), imidazole (3.0 equiv), and diphenylchlorosilane (3.0 equiv), and the resulting homogeneous mixture was allowed to warm to room temperature slowly and stirred for 15 h. The reaction mixture was transferred to a round-bottom flask with hexanes (15 mL) and placed in a freezer (0 °C) for 2 h. The resulting ammonium salts were removed by filtration through Celite, and the filtrate was concentrated in vacuo. The crude product was redissolved in THF (0.2 M relative to the hydroxy ketone substrate) at 0 °C. A solution of TBAF (1.0 M, 9.0 equiv) was then added, and the mixture was warmed to room temperature for 1 h. The reaction was quenched with aq. NH_4Cl (15 mL), and the mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica (1:1 hexanes/ethyl acetate).

*(3R,4S)-4-Phenylpentane-1,3-diol/(3S,4R)-4-Phenylpentane-1,3-diol (**21**).* (0.060 g, 68%, dr >10:1 in favor of the *anti*-propionate product by comparison to literature data[23]). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38−7.30 (m, 2H), 7.26−7.19 (m, 3H), 3.95−3.80 (m, 3H), 2.79 (quin, *J* = 7.0 Hz, 1H), 2.58 (bs, 1H), 2.02 (m, 1H), 1.91−1.85 (m, 1H), 1.70−1.62 (m, 1H), 1.28 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.2, 128.9, 128.8, 128.3, 128.0, 127.1, 62.0, 46.8, 35.8, 17.8 cm^{-1}.

*(3R,4S)/(3S,4S)-4-((4-Methoxybenzyl)oxy)pentane-1,3-diol (**22**).* (0.038 g, 83%, dr ∼1:1). Spectral data for the mixture of stereoisomers: IR (neat): 3378, 2935, 1612, 1513, 1245, 1092, 1032, 821, 730 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, *J* = 9.0 Hz, 4H), 6.88 (d, *J* = 9.0 Hz, 4H), 4.60 (d, *J* = 11.0 Hz, 2H), 4.55 (d, *J* = 11.0 Hz, 1H), 4.42 (d, *J* = 11.0 Hz, 1H), 4.36 (d, *J* = 11.5 Hz, 2H), 3.90 (m, 1H), 3.80 (s, 6H), 3.67 (m, 2H), 3.50 (m, 1H), 3.40 (q, *J* = 5.5 Hz, 2H), 1.75−1.62 (m, 4H), 1.17 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.3, 159.2, 130.4, 130.2, 129.5, 129.3, 78.1, 76.8, 75.0, 73.3, 70.7, 70.4, 61.4, 61.2, 55.3, 34.3, 33.7, 15.3, 14.0.

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HRMS (TOF ESI+) calcd for $[C_{13}H_{20}O_4 + Na]^+$ 263.1259, found 263.1267.

*(3S,4R)-5-((4-Methoxybenzyl)oxy)-4-methylpentane-1,3-diol (**23**).* (0.085 g, 90%, dr 1.4:1 in favor of the (3*S*,4*R*) product by comparison to literature data[25]). Spectral data for the mixture of stereoisomers: IR (neat): 3378, 2935, 1612, 1513, 1245, 1092, 1032, 821, 730 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, J = 7.5 Hz, 4H), 6.88 (d, J = 8.0 Hz, 4H), 4.44 (s, 2H), 4.43 (s, 2H), 3.98 (d, J = 10.0 Hz, 1H), 3.85−3.80 (m, 4H), 3.80 (s, 6H), 3.76 (m, 1H), 3.60 (dd, J = 3.5, 9.0 Hz, 1H), 3.50 (q, J = 7.0 Hz, 2H), 3.43 (t, J = 8.0 Hz, 1H), 3.33 (bs, OH), 3.18 (bs, OH), 2.93 (bs, OH), 1.94−1.86 (m, 2H), 1.80−1.63 (m, 4H), 1.56−1.51 (m, 1H), 0.92 (d, J = 7.0 Hz, 3H), 0.85 (d, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.6, 159.5, 130.1, 129.8, 129.6, 129.5, 114.1, 114.1, 77.6, 75.4, 75.2, 74.3, 73.4, 73.4, 62.4, 61.9, 55.5, 38.7, 38.5, 36.2, 35.2, 29.9, 13.8, 11.6.

*(3S,4R)-5-((tert-Butyldimethylsilyl)oxy)-4-methylpentane-1,3-diol (**24**).* (0.041 g, 83%, dr 2:1 in favor of the (3*S*,4*R*) stereoisomer[26]). Spectral data for the mixture of stereoisomers: IR (neat): 3334, 2954, 2928, 2884, 2857, 1472, 1463, 1525, 1053, 8333, 774 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 4.49 (bs, 2H), 4.03 (d, J = 11.0 Hz, 1H), 3.90−3.75 (m, 7H), 3.67 (dd, J = 6.0, 10.5 Hz, 1H), 3.57 (dd, J = 6.0, 9.5 Hz, 2H), 1.82−1.65 (m, 6H), 1.48 (m, 1H), 0.92 (d, J = 7.5 Hz, 3H), 0.89 (s, 18H), 0.82 (d, J = 6.5 Hz, 3H), 0.08 (s, 6H), 0.07 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 78.2, 75.9, 69.1, 69.3, 62.4, 61.9, 39.8, 39.4, 36.4, 35.4, 26.0, 26.0, 18.3, 18.3, 13.5, 11.1, −5.4, −5.5, −5.5. HRMS (TOF ESI+) calcd for $[C_{12}H_{28}O_3Si + Na]^+$ 271.1705, found 271.1703.

*(R)-1-((4-Methoxybenzyl)oxy)-2-methylpentan-3-one (**25**).* To a solution of (*R*)-methyl 3-((4-methoxybenzyl)oxy)-2-methylpropanoate[40] (4.8 g, 20.0 mmol, 1.0 equiv) and *N*,*O*-dimethylhydroxylamine 4.1) g, 42.0 mmol, 2.1 equiv) in THF (44 mL) at −20 °C was added freshly prepared isopropylmagnesium chloride (28.0 mL, 3.0 M, 4.2 equiv) over 20 min, and the mixture was slowly warmed to 0 °C and stirred for 1 h. The reaction was quenched with aq. NH_4Cl (40 mL), and the mixture was extracted with MTBE (4 × 40 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo, and the crude product was redissolved in THF (140 mL) at 0 °C. Ethylmagnesium bromide (13.3 mL, 3.0M, 2.0 equiv) was added slowly over 5 min, and the mixture was stirred for 45 min. The reaction was quenched with aq. NH_4Cl (50 mL), and the mixture was extracted with MTBE (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica provided compound **25** as a clear pale-yellow oil (4.06 g, 86% over two steps). NMR spectral data matched those reported in the literature:[27] ^1H NMR (500 MHz, $CDCl_3$): δ 7.21 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 4.4 (d, J = 11.0 Hz, 1H), 4.39 (d, J = 11.5 Hz, 1H), 3.80 (s, 3H), 3.59 (dd, J = 8.0, 9.5 Hz, 1H), 3.42 (dd, J = 5.5, 9.5 Hz, 1H), 2.85 (m, 1H), 2.50 (q, J = 7.5 Hz, 2H), 1.06 (d, J = 7.5 Hz, 3H), 1.03 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.9, 159.2, 130.2, 129.2, 113.7, 72.9, 72.1, 55.3, 49.2, 46.2, 35.3, 13.7, 7.6.

*(2R,4R)-1-Hydroxy-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentan-3-one (**26**).* To a solution of dicyclohexylboron chloride (5.2 mL, 1.0 M, 1.3 equiv) in diethyl ether (16 mL) at 0 °C was added triethylamine (0.892 mL, 6.4 mmol, 1.6 equiv) followed by the dropwise addition of compound **25** (0.944 g, 4.0 mmol, 1.0 equiv) as a solution in diethyl ether (8 mL). The mixture was stirred for 2 h and then cooled to −78 °C, and formaldehyde [obtained by pyrolysis of dry paraformaldehyde (1.20 g, 40 mmol, 10.0 equiv)] as a precooled solution in diethyl ether (5 mL) was added via cannula. After 1 h, the solution was warmed to 0 °C, and the reaction was quenched with MeOH (16 mL) and pH 7.0 buffer (16 mL). Hydrogen peroxide (3.0 mL, 30% aq.) was added dropwise, and the mixture was stirred and allowed to warm to room temperature for 1 h. The reaction mixture was extracted with DCM (3 × 50 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica (10:1 to 1:1 hexanes/EtOAc) provided compound **26** as a clear colorless oil (1.10 g, 100%) with approximately 20:1 diastereoseletivity in favor of the (2*R*,4*R*) stereoisomer by comparison to literature data:[41] IR (neat): 3398, 2972, 2936, 2877, 1707, 1612, 1512, 1245, 1173, 1085, 1030, 818 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 4.42 (d, J = 11.5 Hz, 1H), 4.38 (d, J = 11.0 Hz, 1H), 3.80 (s, 3H), 3.77 (m, 1H), 3.69−3.62 (m, 2H), 3.42 (dd, J = 5.0, 9.0 Hz, 1H), 3.12 (m, 1H), 2.88 (m, 1H), 2.52 (t, J = 6.5 Hz, O−H), 1.10 (d, J = 7.5 Hz, 3H), 1.04 (d, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 217.4, 159.3, 129.7, 129.3, 113.8, 73.1, 72.2, 64.6, 55.3, 48.5, 44.1, 13.9, 12.7. HRMS (TOF ESI+) calcd for $[C_{15}H_{22}O_4 + Na]^+$ 289.1416, found 289.1407.

*(2S,4R)-1-Hydroxy-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentan-3-one (**27**).* To a solution of $TiCl_4$ (3.36 mL, 1.0 M, 3.36 mmol, 0.84 equiv) in DCM (4 mL) at 0 °C was added dropwise freshly distilled $Ti(i\text{-}PrO)_4$ (0.331 mL, 1.12 mmol, 0.28 equiv), and the mixture was stirred for 10 min followed by 10 min at room temperature. This mixture was then added via cannula to a solution of compound **25** (0.944 g, 4.0 mmol, 1.0 equiv) in DCM (8 mL) at −78 °C. The resulting mixture was stirred for 2 min, after which $i\text{-}Pr_2NEt$ (0.766 mL, 4.4 mmol, 1.1 equiv) was added and the reaction was stirred for 30 min. Formaldehyde [obtained by pyrolysis of dry paraformaldehyde (1.20 g, 40 mmol, 10.0 equiv)] as a precooled solution in diethyl ether (5 mL) was then added via cannula, and the mixture was stirred for 1.5 h at −78 °C. The reaction was quenched with aq. NH_4Cl (20 mL), and the mixture was stirred vigorously at room temperature for 5 min. MTBE (40 mL) was added along with H_2O (20 mL), saturated $NaHCO_3$ (20 mL), and brine (20 mL). The layers were separated, and the aqueous phase was extracted with MTBE (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica (10:1 to 1:1 hexanes/EtOAc) provided compound **27** as a clear colorless oil (0.620 g, 56%) as a 4:1 mixture of diastereomers in favor of the (2*S*,4*R*) stereoisomer by comparison to literature data.[41] Characteristic signals for the major stereoisomer: IR (neat): 3447, 2970, 2934, 2877, 1707, 1612, 1513, 1458, 1362, 1302, 1245, 1087, 1032, 818 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 4.41 (d, J = 11.5 Hz, 1H), 4.37 (d, J = 12.0 Hz, 1H), 3.80 (s, 3H), 3.77 (m, 1H), 3.69−3.62 (m, 2H), 3.45 (dd, J = 4.5, 8.0 Hz, 1H), 3.19 (m, 1H), 2.90 (m, 1H), 2.71 (t, J = 7.0 Hz, 1H), 1.08 (d, J = 7.5 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 217.6, 159.4, 129.5, 129.4, 113.9, 73.2, 73.0, 65.0, 55.2, 48.9, 45.1, 13.4, 12.7. HRMS (TOF ESI+) calcd for $[C_{15}H_{22}O_4 + Na]^+$ 289.1416, found 289.1407.

*(2R,3S,4R)-5-((4-Methoxybenzyl)oxy)-2,4-dimethylpentane-1,3-diol (**28**).* Prepared according to the general intramolecular hydrosilylation procedure. (0.036 g, 68%, dr >10:1 in favor of the (2*R*,3*S*,4*R*) stereoisomer by comparison to literature data[42]). IR (neat): 3264, 2969, 2935, 2890, 2870, 2839, 1612, 1514, 1299, 1247, 1058, 1039, 1025, 990, 817, 697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 4.46 (s, 1H), 3.81 (s, 3H), 3.80−3.73 (m, 2H), 3.69−3.64 (m, 1H), 3.59 (dd, J = 4.0, 9.5 Hz, 1H), 3.45 (t, J = 9.0 Hz, 1H), 1.99 (m, 1H), 1.75 (m, 1H), 0.98 (d, J = 6.5 Hz, 3H), 0.76 (d, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.4, 129.4, 113.9, 76.5, 73.3, 55.3, 36.3, 35.8, 13.1, 8.7.

*(2S,3R,4R)-5-((4-Methoxybenzyl)oxy)-2,4-dimethylpentane-1,3-diol (**29**).* Prepared according to the general intramolecular hydrosilylation procedure. (0.038 g, 72%, dr >10:1 in favor of the (2*S*,3*R*,4*R*) stereoisomer[43]). IR (neat): 3384, 2963, 2932, 2876, 1612, 1513, 1459, 1245, 1078, 1032, 972, 819 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.23 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 4.42 (s, 2H), 3.80 (s, 3H), 3.78−3.70 (m, 2H), 3.64 (d, J = 5.0 Hz, 2H), 3.44 (d, J = 5.5 Hz, 2H), 1.93 (m, 1H), 1.81 (m, 1H), 1.03 (d, J = 7.0 Hz, 3H), 1.01 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 130.2, 129.4, 113.8, 74.4, 73.0, 67.2, 55.3, 37.7, 36.3, 12.3, 11.6. HRMS (TOF ESI+) calcd for $[C_{15}H_{24}O_4 + Na]^+$ 291.1572, found 291.1579.

*(4S,5S)-4-((R)-1-((4-Methoxybenzyl)oxy)propan-2-yl)-5-methyl-1,3-dioxan-2-one (**29-carbonate**).* To a flask containing compound **29** (0.034 g, 0.127 mmol, 1.0 equiv) in toluene (2.0 mL) was added carbonyldiimidazole (0.023 g, 0.14 mmol, 1.1 equiv), and the mixture was heated to 115 °C for 18 h, cooled to room temperature, and concentrated in vacuo. Purification by flash column chromatography on silica gel (4:1 to 1:1 hexanes/EtOAc) provided **29-carbonate** (0.026 g,

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75%) as a clear colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (d, J = 8.5 Hz, 1H, C(2)), 6.88 (d, J = 9.0 Hz, 1H, C(3)), 4.43 (dd, J = 3, 11 Hz, 1H, C(9)), 4.41 (d, J = 12.0 Hz, 1H, C(4)), 4.38 (d, J = 12.0 Hz, 1H, C(4)), 4.33 (dd, J = 2.5, 9.5 Hz, 1H, C(7)), 4.15 (dd, J = 1.5, 10.5 Hz, 1H, C(9)), 3.81 (s, 3H, C(1)), 3.41 (dd, J = 3.5, 9.5 Hz, 1H, C(5)), 3.34 (dd, J = 5.5, 9.5 Hz, 1H, C(5)), 2.17 (m, 1H, C(8)), 2.00 (m, 1H, C(6)), 1.15 (d, J = 7.0 Hz, 3H, C(10)), 1.11 (d, J = 7.5 Hz, 3H, C(11)). ^{13}C NMR (125 MHz, $CDCl_3$): δ 228.6, 159.3, 148.9, 129.9, 113.8, 84.4, 74.4, 73.0, 71.2, 55.3, 35.9, 35.7, 35.3, 27.7, 14.1, 10.1.

(S)-4-Benzyl-3-((2S,3R,4S,5R,6R)-3,5-dihydroxy-7-((4-methoxybenzyl)oxy)-2,4,6-trimethylheptanoyl)oxazolidin-2-one (30). In an open-air atmosphere, compound **28** (0.054 g, 0.2 mmol, 1.0 equiv) was dissolved in DCM (2 mL) at 0 °C. Saturated aqueous $NaHCO_3$ (1.5 mL) was added, and the mixture was stirred vigorously. Potassium bromide (0.0095 g, 0.08 mmol, 0.4 equiv), TEMPO (0.0031 g, 0.02 mmol, 0.1 equiv), and NaOCl (0.4 mL, 6% aq., 0.4 mmol, 2.0 equiv) were then added, and the mixture was stirred for 20 min. The reaction was quenched with H_2O (10 mL), and the mixture was extracted with DCM (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to provide (2*S*,3*R*,4*R*)-3-hydroxy-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentanal, which was taken directly into the next reaction. To a solution of (*S*)-4-benzyl-3-propionyloxazolidin-2-one (0.114 g, 0.5 mmol, 2.5 equiv) in DCM (3 mL) at 0 °C was added $TiCl_4$ (0.55 mL, 1.0 M, 2.75 equiv), and the mixture was stirred for 5 min. *i*-Pr_2NEt (0.087 mL, 0.5 mmol, 2.5 equiv) was then added dropwise, and the mixture was stirred for 20 min and then cooled to −78 °C. *N*-Methyl-2-pyrrolidone (0.048 mL, 0.5 mmol, 2.5 equiv) was added, and the mixture was stirred for 10 min. (2*S*,3*R*,4*R*)-3-Hydroxy-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentanal (0.046 g, 0.017 mmol, 1.0 equiv) was then added as a solution in DCM (3 mL), and the mixture was stirred for 1 h at −78 °C before warming to 0 °C and stirring for 2 h. The reaction was quenched with aq. NH_4Cl (10 mL), and the mixture was extracted with DCM (3 × 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica (4:1 to 1:1 hexanes/EtOAc) provided compound **30** as a clear colorless oil (0.072 g, 85%) as a 4:1 mixture of diastereomers. IR (neat): 3446, 2968, 1775, 1697, 1612, 1513, 1454, 1382, 1363, 1245, 1209, 1100, 1077, 1032, 970, 910, 824, 760, 729, 701 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (t, J = 7.5 Hz, 2H), 7.28 (d, J = 7.0 Hz, 1H), 7.25 (d, J = 9.0 Hz, 2H), 7.21 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 4.69−4.65 (m, 1H), 4.49 (d, J = 12.0 Hz, 1H), 4.44 (d, J = 11.5 Hz, 1H), 4.22−4.16 (m, 2H), 4.14 (dd, J = 3.0, 9.5 Hz, 1H), 4.09 (q, J = 5.5 Hz, 1H), 4.02−3.95 (m, 2H), 3.80 (s, 3H), 3.62 (d, J = 5.5 Hz, 1H), 3.59 (dd, J = 4.0, 9.0 Hz, 1H), 3.48 (t, J = 9.0 Hz, 1H), 3.31 (dd, J = 3.5, 13.0 Hz, 1H), 2.63 (dd, J = 10.0, 13.0 Hz, 1H), 2.02 (m, 1H), 1.76 (qd, J = 2.0, 7.0 Hz, 1H), 1.29 (d, J = 7.0 Hz, 3H), 1.01 (d, J = 7.0 Hz, 3H), 0.73 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.2, 159.4, 153.0, 135.3, 129.5, 129.4, 129.0, 127.4, 113.9, 76.6, 74.9, 73.3, 66.0, 40.5, 38.2, 36.5, 35.7, 13.0, 12.2, 9.7. HRMS (TOF ESI+) calcd for $[C_{28}H_{37}O_7N + Na]^+$ 522.2468, found 522.2460.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental procedures and ^{1}H and ^{13}C NMR data for compounds **1**−**12** and **14**−**30**. 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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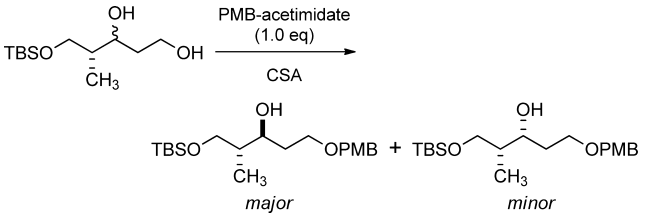
(26) To determine the stereochemistries of the major and minor isomers for **24**, they were converted to the corresponding mono-PMB derivatives: The ^{1}H NMR data were then compared to those for the



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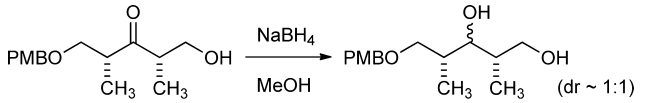
(30) Reduction of compound **26** using $NaBH(OAc)_3$ gave **28** with 90:10 dr (see ref 28).

(31) For comparison, reduction of **27** using $NaBH_4$ proceeded with ∼1:1 ds:



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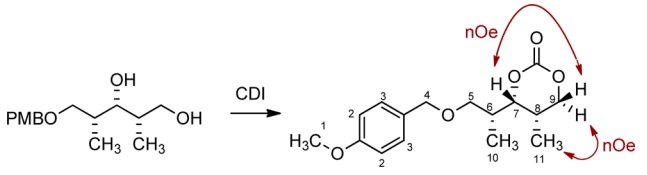
(43) The stereochemistry of the major product was determined by detailed NMR analysis after its conversion to a cyclic carbonate:



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