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Synthesis of the C14−C25 Subunit of Bafilomycin A_1

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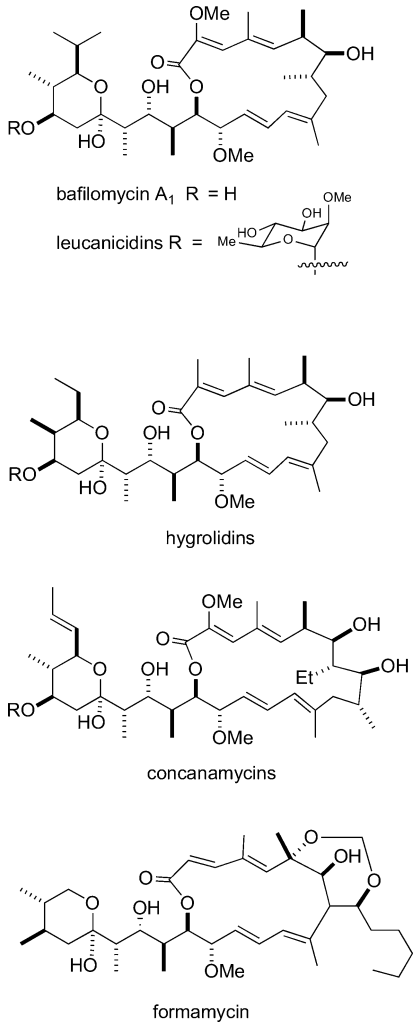
The enantioselective synthesis of the C14−C25 subunit of bafilomycin A_1 was realized in a convergent route. The sequence involves two dynamic kinetic resolution steps of 2-alkyl 1,3-diketones that use optically active ruthenium complexes, an *anti*-selective reduction of a β-hydroxyketone to control the C23 stereogenic center, and an aldol-type reaction under Evans' conditions, which sets the C17 and C18 stereogenic centers.

Introduction

The bafilolides, including bafilomycins[1] and leucanicidins,[2] are members of the plecomacrolide family of macrolide antibiotics that includes concanamycins,[3] hygrolidins,[4] formamicin, and the recently discovered micromonospolides[5] (Scheme 1).[6] Bafilomycin A_1 was isolated from the fermentation broth of *Streptomyces griseus* in 1983[7] and has since shown interesting biological activities. This compound is a potent and specific inhibitor of vacuolar H^+-ATPases (V-ATPases) in vitro and in vivo.[8] Given that V-ATPases are known to participate in bone resorption, inhibitors of such enzymes may potentially be used for the treatment of osteoporosis.[8a,9] Furthermore, this compound displays broad antibacterial and antifungal activity.[10]

SCHEME 1. Molecular Structures of the Plecomacrolide Antibiotics



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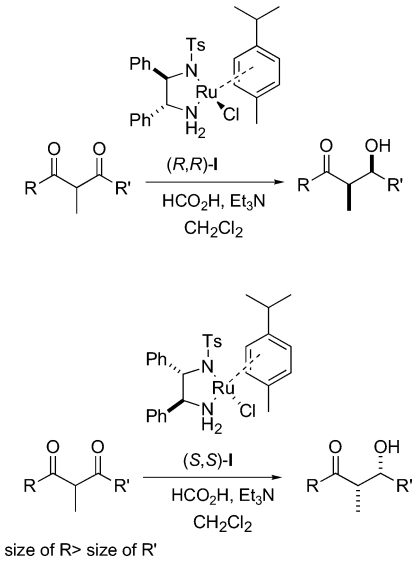
The stereochemistry of bafilomycin A_1 was initially assigned on the basis of molecular modeling and NMR data[11] and was later confirmed by X-ray analysis.[12] The conformation of the molecule in solution has been shown to be indistinguishable from its solid-state conformation.[12b] Bafilomycin A_1 is a 16-membered macrolide with 12 stereogenic centers, two diene units, and an acid- and base-sensitive six-membered hemiketal that participates in a hydrogen-bond network with the C17 hydroxyl group and the carbonyl of the 16-membered lactone, all of which is necessary for biological activity.

In view of the interesting chemical structure and biological properties, considerable effort has been devoted to the development of efficient total syntheses of bafilomycins.[13−17] To date, four total syntheses of bafilomycin A_1[13−16] and one synthesis of bafilomycin V_1 have been reported.[17] Furthermore, several partial syntheses of bafilomycin A_1 and of its analogues have also been published.[18−21]

Somewhat surprisingly, in all of the total syntheses the assembly of the backbone of the molecule followed an identical strategy, as the coupling of the two major fragments C1−C11 and C12−C25 were achieved by Stille reaction and the macrolactonization was realized under Yamaguchi's conditions. However, the differences in the total syntheses were the methods to control the stereogenic centers, which were based either on asymmetric aldolization,[13] crotylborations,[15] allenylzincations,[17] or the use of chiral pools.[14,16]

Previously we described that the dynamic kinetic resolution of 2-alkyl 1,3-diketones by enantioselective monoreduction, using (*R*,*R*)-**I** and (*S*,*S*)-**I** chiral ruthenium catalysts affords *β*-hydroxyketones in high regio-, diastereo-, and enantioselectivity[22] (Scheme 2). As an extension of this work, we wish to report that this dynamic kinetic reduction approach can be used to prepare the C14−C25 fragment of bafilomycin A_1 in a highly convergent and enantioselective manner.

SCHEME 2. Dynamic Kinetic Resolution of 1,3-Diketones



The disconnection of bafilomycin A_1 into fragments **A** and **B** follows the classical strategy used in published syntheses of this molecule. The preparation of fragment **A**, which corresponds to the C14−C25 subunit of bafilomycin, is illustrated in Scheme 3. This approach includes four key steps: an anionic coupling of a dithiane fragment with an alkyl halide to establish the C19−C20 bond; the enantioselective monoreduction of the 2-alkyl 1,3-diketones **3** and **4** to control the stereogenic centers at C15, C16 and C21, C22, respectively; a stereoselective reduction of a *β*-hydroxyketone to set the C23 center; and an aldol-type Evans coupling to control the C17 and C18 stereogenic centers (Scheme 3).

Results and Discussion

Diketones **3** and **4** were prepared in two steps from 2-(benzyloxy)acetic acid **1**. After treatment of **1** with benzotriazole[23] in the presence of DCC (THF, rt), the acylbenzotriazole **2** was isolated in 96% yield. The addition of the lithium enolates of propiophenone and of 2-methyl 1,3-diketone, generated both with LDA at room temperature in THF, to **2** led to the desired diketones **3** (72% yield) and **4** (72% yield), respectively. Diketones **3** and **4** were reduced under asymmetric transfer hydrogenation conditions. When compound **3** was reduced by complex (*R*,*R*)-**I** (1 mol %), Et_3N (2 equiv), and HCO_2H (5 equiv) in CH_2Cl_2 at room temperature for 16 h, a mixture of two separable *β*-hydroxyketones **5** and **5′**[22] were obtained in a ratio of 68/32[24] in 89% yield. The major isomer **5** was formed in an enantiomeric excess of 93%.[25] The relative configuration at C2 and C3, which corresponds to the C15 and C16 stereogenic centers in bafilo-

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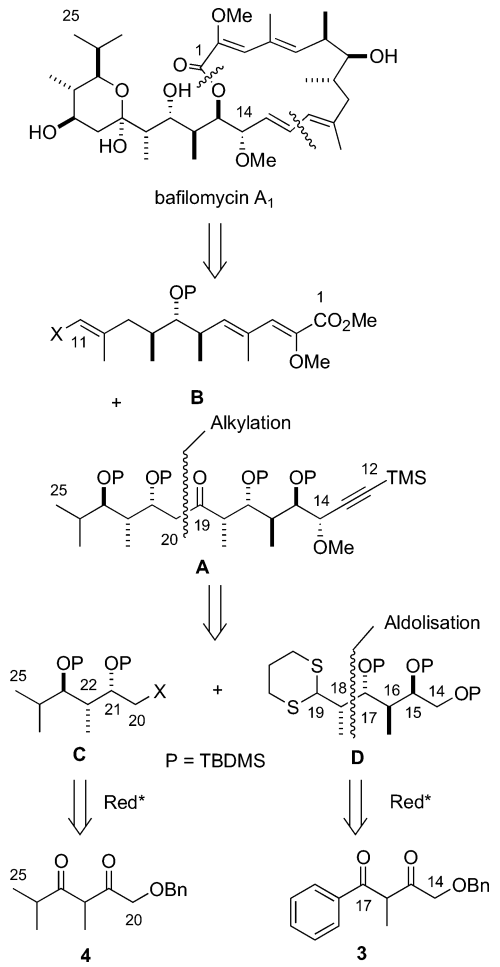
(24) The diastereoselectivity was determined by ^1H NMR analysis.

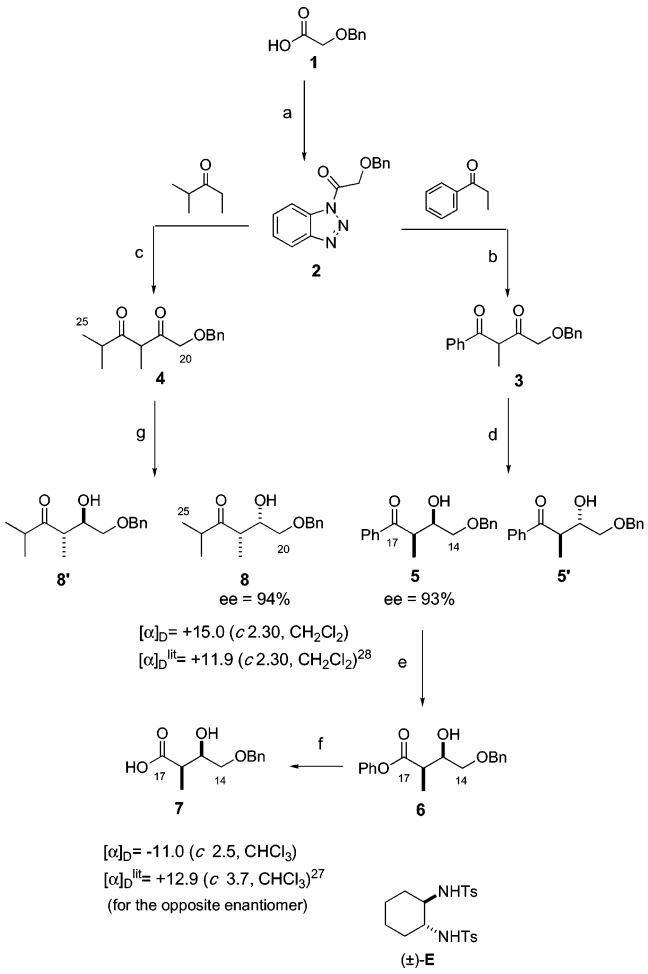
(25) The enantiomeric purity was determined by chiral HPLC: Chiracel OD-H column; eluent, hexane/2 propanol 98/2.

SCHEME 3. Retrosynthetic Analysis of Bafilomycin A_1



mycin A_1, was determined by ^{1}H NMR. The value of coupling constants between the protons at C2 and C3 was $J = 5.9$ Hz, which is representative of a *syn* stereochemistry. Furthermore, the transformation of **5** to the known hydroxyacid **7** confirmed the relative *syn* stereochemistry of the substituents and established the absolute configuration of the stereogenic centers by comparison of their $[\alpha]_D$. The conversion of **5** to **7** was realized in two steps by using a Baeyer−Villiger oxidation[26] [$(TMSO)_2$; $SnCl_4$; (±)-1,2-(tosylaminocyclohexane, CH_2Cl_2, rt, then THF/AcOH/H_2O] followed by saponification of ester **6** [LiOH·H_2O; THF/H_2O]. The acid **7** was isolated in 78% yield and its $[\alpha]^{20}_D$ [−11.0 (*c* 2.5, $CHCl_3$)] was compared with the $[\alpha]^{20}_D$ of the known (2*S*,3*S*)-*β*-hydroxyacid [+12.9 (*c* 3.7, $CHCl_3$)].[27] The comparison of the $[\alpha]^{20}_D$ allowed us to attribute the 2*R* and 3*R* absolute configuration for the stereogenic centers in compound **5**. In parallel, diketone **4** was reduced with the (*S*,*S*)-**I** ruthenium complex (1 mol %) in the presence of a mixture of HCO_2H/Et_3N in CH_2Cl_2. The reaction afforded a mixture of two diastereomers **8** and **8′** in a ratio of 72/28[24] in 92% yield.[22] The enantiomeric excess of 94% for the major isomer **8** was determined by chiral HPLC.[25] The *syn* relative

SCHEME 4[a]



[a] Reagents and conditions: (a) DCC, benzotriazole, rt (96%); (b) LDA, THF (72%); (c) LDA, THF, (72%); (d) (*R*,*R*)-**I**, HCO_2H, Et_3N, CH_2Cl_2, (dr = 68/32, 89%); (e) (1) **E**, $SnCl_2$, $(TMSO)_2$ then AcOH, THF, H_2O (78%); (f) LiOH, THF, H_2O (78%); (g) (*S*,*S*)-**I**, Et_3N, HCO_2H, CH_2Cl_2 (dr = 72/28, 92%).

configuration and the 2*S* and 3*S* absolute configuration was determined by comparison of the $[\alpha]^{20}_D$ of **8** [+15.0, (*c* 2.30, CH_2Cl_2)] with the $[\alpha]^{20}_D$ reported in the literature for the same compound [+11.9, (*c* 2.30, CH_2Cl_2)][28] (Scheme 4). The two optically active *β*-hydroxy ketones **5** and **8** were then transformed into, respectively, the C19−C14 and C20−C25 subunits of bafilomycin A_1.

For the preparation of the C14−C19 subunit and particularly to control the stereogenic centers at C17 and C18, the addition of the (*Z*)-boron enolate **12** derived from Evans' chiral propionyl benzyl-oxazolidinone[29] to aldehyde **11** was planned. It was anticipated that the reaction would proceed with anti-Felkin selectivity with α-substituted aldehydes producing *syn*,*anti*-aldols.[30] Thus, aldehyde **11** was prepared from the previously synthesized *β*-hydroxyester **6** in a three-step sequence (Scheme 5). After protection of the hydroxyl group in **6** as a *tert*-

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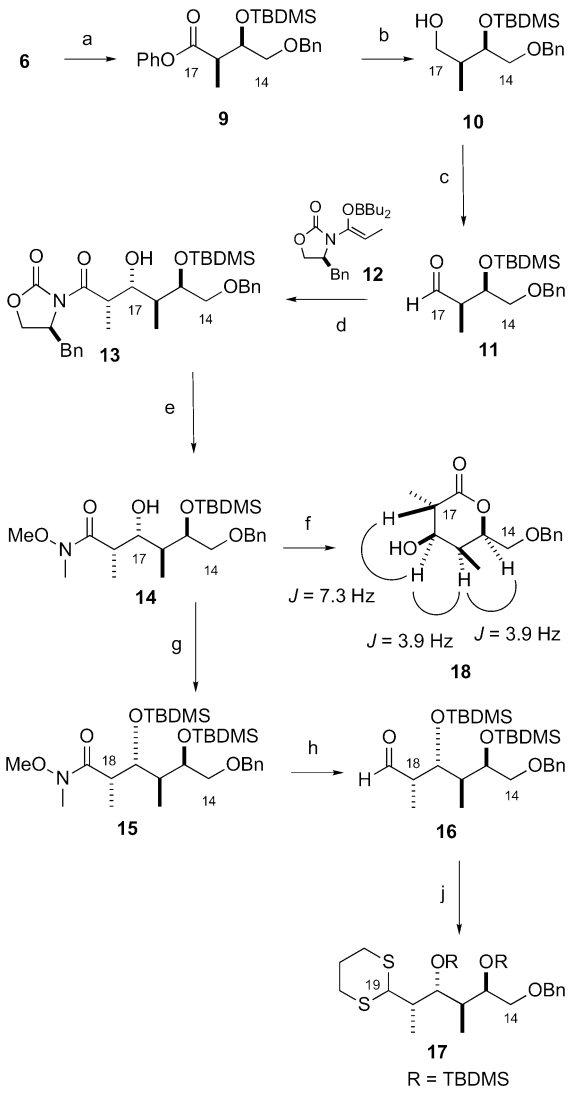
SCHEME 5[a]



[a] Reagents and conditions: (a) TBDMSOTf, 2,6-lutidine, (quant); (b) DIBAL-H, toluene, −78 °C; (quant); (c) Swern (90%); (d) (80%); (e) (MeO)MeNH·HCl, Me_3Al; (97%); (f) HF·Pyr THF, (77%); (g) TBDMSCl, 2,6-lutidine, (97%); (h) DIBAL-H, THF (89%); (i) $HS(CH_2)_3SH$, $TiCl_4$, (98%).

butyldimethylsilyl ether, the ester group in **9** was then reduced by DIBAL-H (toluene, −78 °C) in quantitative yield, and the resulting alcohol **10** was oxidized to the corresponding aldehyde **11** in 90% yield with a Swern reaction [$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C]. When aldehyde **11** was added to the oxazolidine boron enolate **12**, the aldol product **13** was obtained in 80% yield as a single diastereomer (Scheme 5).

The stereochemical confirmation of the aldol **13** was ascertained through lactone **18**, via amide **14**. This latter compound was obtained in 97% yield from oxazolidine **13** by treatment with the aluminum amide of the *N*,*O*-dimethyl hydroxylamine [Me(MeO)NH·HCl, $AlMe_3$, CH_2Cl_2),[31] which after deprotection of the hydroxy groups at C15 (HF/pyridine) cyclized to lactone **18** in 77% yield. The value of the coupling constants in **18**, ($J_{H15-H16}$ = 3.9 Hz, $J_{H16-H17}$ = 3.9 Hz, and $J_{H17-H18}$ = 7.3 Hz) showed a *cis*-relationship between the substituents at C15−C16 and C16−C17 and a *trans*-relationship between the substituents at C17−C18. Consequently, the anti-Felkin type aldolization was confirmed, producing a *syn*,*anti*,-*syn*-stereotetrad. Having obtained the desired absolute configurations for the stereogenic centers in amide **14**, the hydroxy group at C17 was protected as a *tert*-butyldimethylsilyl ether with TBDMSOTf (2,6-lutidine, CH_2Cl_2, −30 °C, 97% yield), and the resulting amide **15** was reduced with DIBAL-H to produce aldehyde **16** in 89% yield. Different conditions were tested to convert aldehyde **16** to thioketal **17**. When BF_3·OEt_2 was used in the presence of propane-1,3-dithiol, degradation of the substrate was observed. On the contrary, the use of $TiCl_4$ in CH_2Cl_2 at −78 °C afforded the desired product **17** in 98% yield (Scheme 5).

The synthesis of iodide **23** corresponding to the C20−C25 subunit of bafilomycin was realized from *β*-hydroxyketone **8**. To set the required *syn*,*anti*-stereotriad of the fragment, *β*-hydroxyketone **8** was reduced by $Me_4NBH(OAc)_3$ in acetic acid.[32] Under these conditions, an inseparable mixture of 1,3-diols **19** (*anti*,*syn*) and **19′** (*syn*,*syn*) was obtained in a ratio of 90/10 in 76% yield. To separate the two isomers and also to establish the relative stereochemistry of the hydroxyl groups at C21 and C23, the mixture of 1,3-diols was transformed to the corresponding acetonides **20** and **20′** using 2,2-dimethoxypropane in the presence of CSA in acetone (dr = 90/10, 74%). The ^{13}C NMR analysis of the major isomer **20** confirmed the *anti*-relationship between the two hydroxy groups.[33] As the ketal protecting group in **20** revealed unsuitable for further transformations, compounds **19** and **19′** were treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) in the presence of 2,6-lutidine to afford after purification the corresponding bis-*tert*-butyldimethylsilyl ether **21**. After cleavage of the benzyl ether (H_2, Pd/C, K_2CO_3, AcOEt), alcohol **22** was obtained in 71% yield and transformed to iodide **23** in 95% yield under Garegg's conditions[34] (Scheme 6).

The coupling of subunit C14−C19 to fragment C20−C25 was realized under Hanessian's conditions.[16b] The generation of the dithiane anion from **17** with *tert*-butyllithium in HMPA proceeded at −78 °C, and after addition of iodide **23**, the coupling product **24** was isolated in a nonoptimized 28% yield (Scheme 7).

Conclusion

In summary, the synthesis of the C14−C25 fragment of bafilomycin A_1 was realized in 11 steps in a sequence involving two enantioselective transfer-hydrogenation steps induced by chiral Ru-complexes. These reactions set the C15, C16, C21, and C22 stereogenic centers in a dynamic kinetic resolution. The synthesis also involves an *anti*-selective reduction of a *β*-hydroxyketone to control the C23 stereogenic center and an aldol-type reaction under Evans' conditions, which sets the C17 and

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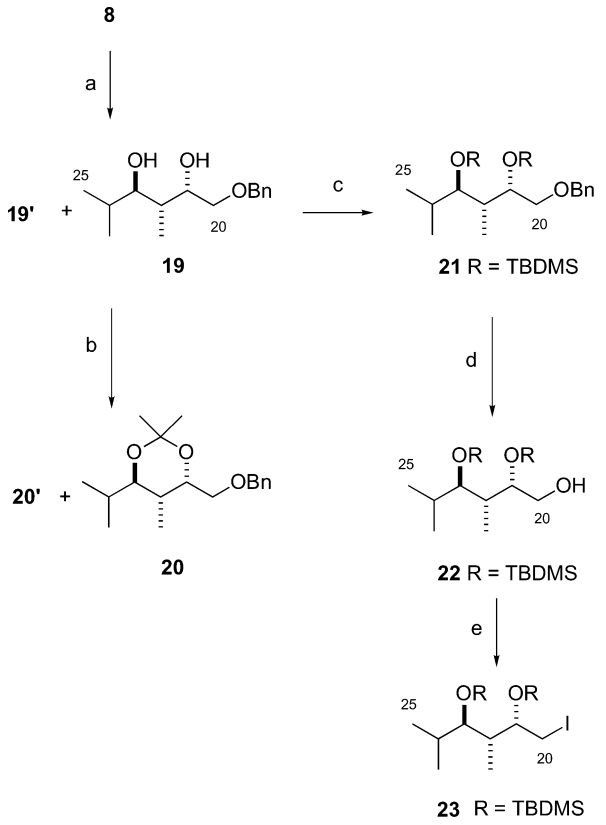
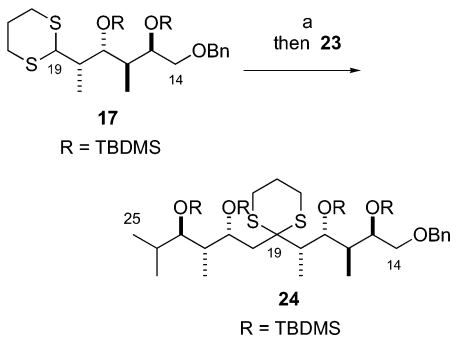
SCHEME 6[a]



[a] Reagents and conditions: (a) $Me_4NBH(OAc)_3$, AcOH (dr = 90/10, 76%); (b) 2,2-DMP, CSA, acetone (74%); (c) TBDMSOTf, 2,6-lutidine (90%); (d) H_2,Pd/C (10%) K_2CO_3, AcOEt (71%); (e) I_2, imidazole, PPh_3, toluene (95%).

SCHEME 7[a]



[a] Reagents and conditions: (a) *t*-BuLi, HMPA, THF (28%).

C18 stereogenic centers. With subunit C14−C25 in hand, progress toward the total synthesis of bafilomycin A_1 continues and will be reported in due course.

Experimental Section

General Procedures. Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. THF and diethyl ether were distilled from sodium/benzophenone immediately before use. CH_2Cl_2, DMF, DMSO, Et_3N, and diisopropylamine were distilled from CaH_2 under argon. Moisture-sensitive reactions were conducted in oven- or flame-dried glassware under an argon atmosphere. Flash chromatography was carried out on Kieselgel 60 (230−400 mesh), and analytical thin-layer chromatography was performed on precoated silica gel (60 F254). Melting points are uncorrected. Mass spectra were obtained by GC/MS with electron impact ionization at 70 eV. Only selected ions are reported. Optical rotations were measured on a Perkin-Elmer 343 polarimeter. ^1H and ^{13}C spectra were recorded at 300 and 75 MHz, respectively. Spectra were recorded in $CDCl_3$, and chemical shifts (δ) are expressed in ppm relative to residual $CHCl_3$ at $\delta = 7.27$ ppm for ^1H and to $CDCl_3$ at $\delta = 77.1$ ppm for ^{13}C. ^1H NMR J values are given in Hz. IR spectrum were recorded as neat films (NaCl cell) and KBr pellets for solids.

(±)-1-(1*H*-Benzotriazol-1-yl)-2-benzyloxyethan-1-one (2). To a solution of benzyloxyacetic acid **1** (2.49 g, 15.0 mmol, 1 equiv) in THF (60 mL) at 0 °C were added 1*H*-1,2,3-benzotriazole (1.78 g, 15.0 mmol, 1 equiv) and a solution of DCC (1.79 g, 15.0 mmol, 1 equiv) in THF (10 mL). After 12 h at room temperature, the solution was filtered through Celite, and the filtrate washed with an aqueous solution of HCl (2 N). The organic phase was dried over $MgSO_4$, filtered, evaporated, and purified by flash chromatography on silica gel (petroleum ether/AcOEt 4/1) to give **2** as a white solid (3.84 g, 96%). $R_f = 0.44$ (petroleum ether/EtOAc 4/1). Mp: 67 °C. IR (film): 1750, 1485, 1450, 1400 cm^{-1}. ^1H NMR: δ 8.17 (dt, 1H, J = 7.0 and 1.0 Hz), 8.00 (dt, 1H, J = 8.5 and 1.0 Hz), 7.56 (ddd, 1H, J = 8.3, 7.2 and 1.1 Hz), 7.42 (ddd, 1H, J = 8.3, 5.9 and 1.3 Hz), 7.40−7.24 (m, 5H), 5.14 (s, 2H), 4.76 (m, 2H). ^{13}C NMR: δ 168.5, 145.4, 136.6, 130.4, 130.3, 128.2, 127.8, 126.0, 119.8, 113.6, 73.4, 68.3. MS (EI, 70 eV) *m*/*z* (rel intensity): 238 ($[MH - N_2]^{+\cdot}$, 16), 180 (13), 162 (10), 146 (42), 118 (29), 91 (100), 65 (12). Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.65; H, 5.19; N, 15.64.

(±)-4-Benzyloxy-2-methyl-1-phenylbutane-1,3-dione (3). To a solution of lithium diisopropylamide (32.9 mmol, 1.1 equiv) in THF (220 mL) at −78 °C was added dropwise a solution of propiophenone (4.29 mL, 32.9 mmol, 1.1 equiv) in THF (150 mL). After 1 h at −78 °C, a solution of acylbenzotriazole **2** (7.98 g, 29.9 mmol, 1 equiv) in THF (100 mL) was added. After 15 min at −78 °C and 1.5 h at room temperature, the reaction mixture was quenched with H_2O and extracted with ether (3 times). The organic phases were dried over $MgSO_4$, evaporated, and purified by flash chromatography on silica gel (petroleum ether/EtOAc 9/1) to give **3** as a white solid (6.08 g, 72%). $R_f = 0.25$ (petroleum ether/EtOAc 9/1). Mp: <50 °C. IR ($CHBr_3$): 1725, 1670, 1595, 1450 cm^{-1}. ^1H NMR: δ 7.99−7.93 (m, 2H), 7.63−7.56 (m, 1H), 7.50−7.42 (m, 2H), 7.26−7.16 (m, 3H), 7.11−7.05 (m, 2H), 4.80 (q, 1H, J = 7.0 Hz), 4.41 (s, 2H), 4.10 (s, 2H), 1.39 (d, 3H, J = 7.0 Hz). ^{13}C NMR: δ 205.9, 197.7, 136.7, 135.7, 133.3, 128.7, 128.6, 128.5, 128.0, 127.7, 73.9, 73.5, 51.4, 12.6. MS (EI, 70 eV) *m*/*z* (rel intensity): 283 ($MH^{+\cdot}$, 0.1), 176 (53), 148 (7), 105 (100), 91 (80), 77 (28), 51 (6). HRMS (CI^+, CH_4): calcd for $C_{18}H_{19}O_3$ ($MH^{+\cdot}$) 283.1334, found 283.1332.

(±)-1-Benzyloxy-3,5-dimethylhexane-2,4-dione (4). To a solution of lithium diisopropylamide (6.18 mmol, 1.1 equiv) in THF (41 mL) at −78 °C was added dropwise a solution of 2-methylpentan-3-one (0.763 mL, 6.18 mmol, 1.1 equiv) in THF (28 mL). After 1 h at −78 °C, a solution of acylbenzotriazole **2** (1.5 g, 5.62 mmol, 1.0 equiv) in THF (19 mL) was added. After 15 min at −78 °C and 1.5 h at room temperature, the reaction mixture was quenched with H_2O and extracted with ether (3 times). The organic phases were dried over $MgSO_4$, evaporated, and purified by flash chromatography on silica gel (petroleum ether/EtOAc 9/1) to give **4** as a colorless liquid (1.00 g, 72%). R_f = 0.27 (petroleum ether/EtOAc 9/1). ^1H NMR: δ 7.39−7.26 (m, 5H), 4.55 (d, 1H, J = 12.2 Hz), 4.51 (d, 1H, J = 12.2 Hz), 4.09 (q, 1H, J = 7.2 Hz), 4.05 (d_{app}, 2H, J = 1.5 Hz), 2.78 (qq, 1H, J = 6.9 and 6.9 Hz), 1.27 (d, 3H, J = 7.2 Hz), 1.09 (d, 3H, J = 6.9 Hz), 1.08 (d, 3H, J = 6.9 Hz). ^{13}C NMR: δ 211.1, 205.5, 136.8, 128.5, 128.0, 127.9, 74.1, 73.5, 54.5, 40.3, 18.3, 18.3, 12.2. MS (EI, 70 eV) *m*/*z* (rel intensity): 177 ($[M - (CH_3)_2CHC{=}O]^{+\cdot}$, 0.37), 142 (29), 91 (100), 71 (37),

65 (6). HRMS (CI^+, CH_4): calcd for $C_{15}H_{21}O_3$ ($MH^{+\bullet}$) 249.1491, found 249.1495.

General Procedure for the Monoreduction of Diketones 3 and 4. The ruthenium complex (*R*,*R*)-**I** or (*S*,*S*)-**I** (1 mol %) was added to a mixture of diketone (1 equiv) in a CH_2Cl_2 solution which was degassed three times. After 16 h at room temperature, the reaction mixture was washed with water (3 times), and the aqueous phases were extracted with CH_2Cl_2 (3 times). The organic phases were combined, dried over $MgSO_4$, and evaporated, and the residue was purified by flash chromatography on silica gel.

(−)-(2*R*,3*R*)-4-Benzyloxy-3-hydroxy-2-methyl-1-phenylbutan-1-one[35] **(5) and (−)-(2*S*,3*R*)-4-benzyloxy-3-hydroxy-2-methyl-1-phenylbutan-1-one (5′).** Diketone **3** (0.2 g, 0.893 mmol, 1 equiv), (*R*,*R*)-**I** (0.236 mL, 0.03 M in CH_2Cl_2, 7.09 μmol, 0.01 equiv), Et_3N (0.199 mL, 1.42 mmol, 2 equiv), HCO_2H (0.136 mL, 3.55 mmol, 5 equiv). Purification by flash chromatography (CH_2Cl_2/diethyl ether 96/4). **(−)-5**: R_f = 0.42 (CH_2Cl_2/diethyl ether: 96/4). ee = 93%.[36] $[\alpha]^{20}_D = -30.0$ (*c* 1.1, CH_2Cl_2). IR (film): 3420, 1670, 1595, 1575, 1445, 1360, 1210 cm^{-1}. ^1H NMR: δ 8.01−7.93 (m, 2H), 7.64−7.56 (m, 1H), 7.52−7.44 (m, 2H), 7.35−7.24 (m, 5H), 4.51 (s, 2H), 4.23 (m, 1H), 3.74 (qd, 1H, *J* = 7.2 and 5.5 Hz), 3.57 (dd, 1H, *J* = 9.6 and 5.1 Hz), 3.50 (dd, 1H, *J* = 9.6 and 5.9 Hz), 2.91 (d, 1H, *J* = 4.4 Hz, OH), 1.29 (d, 3H, *J* = 7.2 Hz). ^{13}C NMR: δ 204.4, 137.8, 136.2, 133.3, 128.7, 128.5, 128.4, 128.2, 127.7, 73.4, 71.6, 71.1, 42.6, 12.8. MS (CI^+, CH_4) *m*/*z* (rel intensity): 285 ($MH^{+\bullet}$, 33), 267 (20), 177 (70), 168 (22), 163 (25), 159 (23), 136 (37), 135 (100), 105 (48). Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.05; H, 7.09. **(−)-5′**: R_f = 0.43 (CH_2Cl_2/diethyl ether: 96/4). ee = nd. $[\alpha]^{20}_D = -36.0$ (*c* 1, CH_2Cl_2). IR (film): 3420, 1670, 1595, 1575, 1445, 1360, 1210 cm^{-1} ^1H NMR: δ 8.01−7.93 (m, 2H), 7.63−7.56 (m, 1H), 7.52−7.44 (m, 2H), 7.36−7.22 (m, 5H), 4.54 (d, 1H, *J* = 11.9 Hz), 4.49 (d, 1H, *J* = 11.9 Hz), 4.10 (qd, 1H, *J* = 6.5 and 6.5 Hz), 3.83 (qd, 1H, *J* = 7.3 and 6.1 Hz), 3.62 (dd, 1H, *J* = 9.6 and 5.5 Hz), 3.57 (dd, 1H, *J* = 9.6 and 5.0 Hz), 3.27 (d, 1H, *J* = 6.6 Hz, OH), 1.25 (d, 3H, *J* = 7.3 Hz); ^{13}C NMR: δ 205.1, 137.8, 136.7, 133.3, 128.6, 128.5, 128.4, 127.7, 73.5, 73.0, 72.1, 42.1, 14.9. HRMS (CI^+, CH_4): calcd for $C_{18}H_{21}O_3$ ($MH^{+\bullet}$) 285.1491, found 285.1487.

(−)-(4*S*,5*S*)-6-Benzyloxy-2,4-dimethylhexan-5-hydroxy-3-one (8) and **(+)−(4*R*,5*S*)-6-benzyloxy-2,4-dimethylhexan-5-hydroxy-3-one (8′).** Diketone **4** (0.2 g, 0.806 mmol, 1 equiv), (*S*,*S*)-**I** (0.269 mL, 0.03 M in CH_2Cl_2, 8.06 μmol, 0.01 equiv), Et_3N (0.226 mL, 1.61 mmol, 2 equiv), HCO_2H (0.155 mL, 4.03 mmol, 5 equiv). Purification by flash chromatography (CH_2Cl_2/diethyl ether 96/4). **(−)-8**: R_f = 0.21 (petroleum ether/diethyl ether: 6/4). ee = 94%.[37] $[\alpha]^{20}_D = -15.0$ (*c* 2.3, CH_2Cl_2). IR (film): 3440, 1705 cm^{-1}. ^1H NMR δ: 7.40−7.25 (m, 5H), 4.53 (s_{app}, 2H), 4.08−4.00 (m, 1H), 3.48 (dd, 1H, *J* = 9.6 and 4.8 Hz), 3.42 (dd, 1H, *J* = 9.6 and 6.2 Hz), 2.97 (qd, 1H, *J* = 7.0 and 5.6 Hz), 2.76 (qq, 1H, *J* = 6.7 and 6.7 Hz), 2.74 (bs, 1H, OH), 1.15 (d, 3H, *J* = 7.0 Hz), 2.09 (d, 3H, *J* = 6.7 Hz), 1.07 (d, 3H, *J* = 6.7 Hz). ^{13}C NMR: δ 218.4, 137.8, 128.4, 127.8, 127.7, 73.4, 71.6, 70.8, 46.0, 40.3, 18.1, 17.9, 12.0. MS (CI^+, CH_4) *m*/*z* (rel intensity): 251 ($MH^{+\bullet}$, 86), 233 (44), 143 (100), 119 (23), 101 (50). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.83; H, 9.05. HRMS (CI^+, CH_4): calcd for $C_{15}H_{23}O_3$ ($MH^{+\bullet}$) 251.1647, found 251.1643. **(+)-8′**: R_f = 0.25 (petroleum ether/diethyl ether 6/4). ee = 85%.[37] $[\alpha]^{20}_D = +20.0$ (*c* 1.0, CH_2Cl_2). IR (film): 3440, 1705 cm^{-1}. ^1H NMR: δ 7.40−7.27 (m, 5H), 4.57 (d, 1H, *J* = 11.8 Hz), 4.52 (d, 1H, *J* = 11.8 Hz), 3.89 (m, 1H), 3.51 (d_{app}, 2H, *J* = 5.1 Hz), 3.08 (bs, 1H, OH), 3.02 (qd, 1H, *J* = 7.0 Hz), 2.74 (qq, 1H, *J* = 7.2 and 7.2 Hz), 1.10 (d, 6H, *J* = 7.2 Hz), 1.07 (d, 3H, *J* = 7.0 Hz). ^{13}C NMR: δ 219.1, 137.8, 128.4, 127.8, 127.4, 73.5, 72.9, 72.2, 45.8, 41.0, 17.8, 14.1. MS (CI^+, CH_4) *m*/*z* (rel intensity): 251 ($MH^{+\bullet}$, 86), 233 (44), 143 (100), 119 (23), 101 (50). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.84; H, 8.92.

(−)-Phenyl (2*R*,3*R*)-4-Benzyloxy-3-hydroxy-2-methylbutanoate (6). To a mixture of molecular sieves 4 Å (1 g) and racemic *trans*-*N*,*N*′-bis(*p*-toluenesulfonyl)cyclohexan-1,2-diamine (0.223 g, 0.532 mmol, 0.8 equiv) at 0 °C were added successively $SnCl_4$ (5.32 mL, 1 M in CH_2Cl_2, 5.32 mmol, 0.8 equiv) and bis(trimethylsilylperoxide) (53.2 mL, 1 M in CH_2Cl_2, 53.2 mmol, 8 equiv). After 10 min at 0 °C, a solution of β-hydroxyketone **5** (1.89 g, 6.65 mmol, 1 equiv) in CH_2Cl_2 (35 mL) was added. After 12 h at room temperature, the reaction was cooled to 0 °C and quenched with a saturated aqueous $NaHCO_3$ solution (23.6 mL) followed by the addition of sodium thiosulfate (7.83 g). After 3 h at room temperature, the reaction mixture was filtered through Celite, and the filtrate was washed with an aqueous HCl (1 N) solution, followed by brine. The organic phases were dried over Na_2SO_4 and evaporated. The residue was dissolved in a mixture of THF/H_2O (37 mL/10 mL) and acetic acid (2.8 mL). After stirring for 18 h at room temperature, the reaction mixture was washed with a saturated aqueous $NaHCO_3$ solution (2 times), the aqueous phases were washed with ether (2 times). The organic phases were gathered and washed with a HCl (1 N) aqueous solution and then with brine, and finally they were evaporated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 2/1) to give **6** as a pale yellow oil (1.55 g, 78%). R_f = 0.26 (petroleum ether/EtOAc 4/1). $[\alpha]^{20}_D = -24.8$ (*c* 1.0, CH_2Cl_2). IR (film): 3440, 1745, 1590, 1490, 1450, 1190, 1160 cm^{-1}. ^1H NMR: δ 7.45−7.19 (m, 8H), 7.10−6.95 (m, 2H), 4.60 (s_{app}, 2H), 4.22 (m, 1H), 3.68−3.56 (m, 2H), 2.95 (dq, 1H, *J* = 7.0 and 5.5 Hz), 2.84 (bd, 1H, *J* = 4.8 Hz, OH), 1.39 (d, 3H, *J* = 7.0 Hz). ^{13}C NMR: δ 173.5, 150.5, 137.7, 129.3, 128.4, 127.8, 125.8, 121.4, 73.5, 71.2, 70.9, 42.3, 12.0. MS (EI, 70 eV) *m*/*z* (rel intensity): 207 ([M − PhO]$^{+\bullet}$, 4), 184 (6), 121 (2), 107 (2), 95 (2), 94 (8), 92 (9), 91 (100), 85 (4), 77 (2), 65 (5). Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.84; H, 6.83.

(−)-(2*R*,3*R*)-4-Benzyloxy-3-hydroxy-2-methylbutanoic Acid (7). To a solution of β-hydroxyester **6** (0.05 g, 0.167 mmol, 1 equiv) in THF (1 mL) was added a solution of LiOH·H_2O (35 mg, 0.833 mmol, 5 equiv) in H_2O (0.5 mL). After 15 min at room temperature, the reaction was diluted with H_2O and Et_2O, and the reaction mixture was extracted with Et_2O (3 times). The aqueous phase was acidified with a 2 N HCl aqueous solution until pH = 3 and extracted with CH_2Cl_2 (5 times). The organic phases were dried over $MgSO_4$, filtered, and evaporated, and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 9/1) to produce **7** as a colorless oil (29 mg, 78%). R_f = 0.31 (CH_2Cl_2/MeOH 9/1). $[\alpha]^{20}_D = -11.0$ (*c* 2.5, $CHCl_3$). IR (film): 3400, 1710, 1450, 1210, 1095 cm^{-1}. ^1H NMR: δ 7.41−7.28 (m, 5H), 4.56 (s_{app}, 2H), 4.19−4.09 (m, 1H), 3.60−3.50 (m, 2H), 2.72 (dq, 1H, *J* = 7.0 and 5.5 Hz), 1.23 (d, 3H, *J* = 7.0 Hz). ^{13}C NMR: δ 179.9, 137.6, 128.5, 127.9, 127.7, 73.5, 71.4, 70.6, 41.8, 11.6. MS (EI, 70 eV) *m*/*z* (rel intensity): 224 ($M^{+\bullet}$, 0.7), 178 (2), 107 (18), 103 (11), 91 (100), 85 (25), 65 (9). HRMS (CI^+, CH_4): calcd for $C_{12}H_{17}O_4$ ($MH^{+\bullet}$) 225.1127, found 225.1126.

(−)-Phenyl (2*R*,3*R*)-4-Benzyloxy-3-(*tert*-butyldimethylsiloxy)-2-methylbutyrate (9). To a solution of β-hydroxy ester **6** (0.8 g, 2.67 mmol, 1 equiv) in CH_2Cl_2 (36 mL) at −78 °C were added TBDMSOTf (0.919 mL, 4.34 mmol, 1.5 equiv) and 2,6-lutidine (0.930 mL, 8.68 mmol, 3 equiv). After 1 h at −78 °C, the reaction was quenched with a saturated aqueous NH_4Cl solution and extracted with $CHCl_3$ (3 times). The organic phases were dried over $MgSO_4$ and evaporated, and the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 9/1 to give **9** as a colorless oil (1.1 g, 100%). R_f = 0.53 (petroleum ether/EtOAc 9/1). $[\alpha]^{20}_D = -3.7$ (*c* 0.75, CH_2Cl_2). IR (film): 1760, 1590, 1490, 1455, 1380, 1360, 1250, 1190 cm^{-1}. ^1H NMR: δ 7.43−7.31 (m, 8H), 7.11−7.04 (m, 2H), 4.63 (d, 1H, *J* = 12.1 Hz), 4.56

(35) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron* **1984**, *40*, 4327.
(36) Column: Daicel CHIRALCEL OD-H. Eluent: *n*-hexane/2-propanol 98/2. Flow rate: 1 mL/min^{-1}. λ = 220 nm.
(37) Column: Daicel CHIRALCEL OJ-H. Eluent: *n*-hexane/2-propanol 98/2. Flow rate: 1 mL/min^{-1}. λ = 220 nm.

(d, 1H, J = 12.1 Hz), 4.47−4.38 (dt, 1H, J = 6.6 and 5.0 Hz), 3.59 (dd, 1H, J = 9.8 and 5.5 Hz), 3.53 (dd, 1H, J = 9.8 and 6.6 Hz), 3.00 (qd, 1H, J = 7.2 and 5.0 Hz), 1.35 (d, 3H, J = 7.2 Hz), 0.94 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H). ^{13}C NMR: δ 173.3, 150.8, 138.0, 129.3, 128.4, 127.8, 127.7, 125.5, 121.5, 73.4, 72.7, 71.7, 43.5, 25.8, 18.1, 11.4, −4.2, −4.9. MS (CI^+, CH_4) m/z (rel intensity): 415 ($MH^{+\bullet}$, 24), 339 (23), 357 (24), 321 (100), 231 (19). Anal. Calcd for $C_{24}H_{34}O_4Si$: C, 69.53; H, 8.26. Found: C, 69.42; H, 8.40.

(+)-(2*S*,3*R*)-4-Benzyloxy-3-(*tert*-butyldimethylsiloxy)-2-methylbutan-1-ol (10). To a solution of ester **9** (0.422 g, 1.02 mmol, 1 equiv) in toluene (16 mL) at −78 °C was added dropwise a solution of DIBAL-H in hexane (3.06 mL, 1 M in hexane, 3.06 mmol, 3 equiv). After 1 h at −78 °C, the reaction was quenched by addition of a saturated aqueous sodium and potassium tartrate solution. The aqueous phase was extracted with ether (3 times), the organic phases were dried over $MgSO_4$ and evaporated, and the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 4/1) to give alcohol **10** as a colorless oil (0.330 g, 100%). R_f = 0.28 (petroleum ether/EtOAc 9/1). $[\alpha]^{20}_D$ = +9.0 (c 1.0, CH_2Cl_2). IR (film): 3320, 1610, 1590, 1470, 1250 cm^{-1}. ^{1}H NMR: δ 7.38−7.27 (m, 5H), 4.56 (d, 1H, J = 11.9 Hz), 4.51 (d, 1H, J = 11.9 Hz), 3.97 (td_{app}, 1H, J = 5.4 and 3.8 Hz), 3.60 (d, 2H, J = 6.2 Hz), 3.50 (d, 2H, J = 5.4 Hz), 2.48 (bs, 1H, OH), 2.05−1.89 (m, 1H), 0.89 (s, 9H), 0.88 (d, 3H, J = 6.6 Hz), 0.08 (s, 3H), 0.06 (s, 3H). ^{13}C NMR: δ 138.1, 128.4, 127.6, 73.4, 72.3, 65.5, 39.2, 25.8, 18.1, 11.7, −4.3, −5.0. MS (EI, 70 eV) m/z (rel intensity): 325 ($MH^{+\bullet}$, 0.01), 203 (13), 175 (14), 145 (6), 21 (100), 73 (10). Anal. Calcd for $C_{18}H_{32}O_3Si$: C, 66.62; H, 9.94. Found: C, 66.64; H, 9.90.

(2*R*,3*R*)-4-Benzyloxy-3-(*tert*-butyldimethylsiloxy)-2-methylbutanal (11). To a solution of oxalyl chloride (0.475 mL, 5.53 mmol, 2.2 equiv) in CH_2Cl_2 (37 mL) at −78 °C was added DMSO (0.504 mL, 7.03 mmol, 2,8 equiv). After 30 min, a solution of alcohol **10** (0.814 g, 2.51 mmol, 1 equiv) in CH_2Cl_2 (10 mL) was added. The reaction mixture was stirred for 20 min at −78 °C, at which time Et_3N (1.66 mL, 11.8 mmol, 4.7 equiv) was added. After 15 min at −78 °C, 15 min at 0 °C, the reaction mixture was quenched with a saturated aqueous NaCl solution and extracted with petroleum ether (3 times). The organic phases were dried over $MgSO_4$ filtered, and evaporated, and the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 9/1) to give aldehyde **11** as a colorless oil (0.750 g, 90%), which was immediately used in the following reaction. R_f = 0.35 (petroleum ether/EtOAc 9/1). IR (film): 3460, 1740, 1690, 1480 cm^{-1}. ^{1}H NMR: δ 9.75 (d, 1H, J = 1.0 Hz), 7.40−7.28 (m, 5H), 4.55 (d, 1H, J = 11.9 Hz), 4.50 (d, 1H, J = 11.9 Hz), 4.33 (ddd, 1H, J = 6.5, 5.2 and 3.8 Hz), 3.50 (dd, 1H, J = 9.6 and 5.2 Hz), 3.42 (dd, 1H, J = 9.6 and 6.5 Hz), 2.61 (qdd, 1H, J = 7.0, 3.8 and 1.0 Hz), 1.07 (d, 3H, J = 7.0 Hz), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C NMR: δ 204.3, 137.9, 128.4, 127.7, 127.6, 73.4, 71.8, 70.5, 50.0, 25.7, 18.0, 7.6, −4.3, −5.0. MS (EI, 70 eV) m/z (rel intensity): 321 ($[M - H]^{+\bullet}$, 0.35), 215 (11), 199 (8), 173 (8), 117 (14), 91 (100), 73 (10). HRMS (CI^+, NH_3): calcd for $C_{18}H_{34}O_3NSi$ $[M + NH_4]^{+\bullet}$ 340.2308, found 340.2310.

(+)-(4*S*)-3-[(2*S*,3*R*,4*S*,5*R*)-6-Benzyloxy-5-(*tert*-butyldimethylsiloxy)-3-hydroxy-2,4-dimethyl-hexanoyl]-4-benzyloxalidin-2-one (13). To a solution of propionyl (5*S*)-5-benzyl oxazolidinone[29] (0.160 g, 0.688 mmol, 1 equiv) in CH_2Cl_2 (1.5 mL) at 0 °C were added dropwise Bu_2BOTf (0.206 mL, 0.812 mmol, 1.18 equiv) and Et_3N (0.125 mL, 0.908 mmol, 1.32 equiv) After 20 min, the reaction mixture was cooled to −78 °C, and aldehyde **9** (0.246 g, 0.764 mmol, 1.1 equiv) in CH_2Cl_2 (0.3 mL) was added dropwise. After 1 h at −78 °C and 2 h at 0 °C, a buffered phosphate solution (pH = 7, 0.756 mL) was added followed by the addition of MeOH (2.27 mL) and a mixture of 30% H_2O_2/MeOH 2/1. After 1 h at 0 °C, the reaction mixture was concentrated under vacuum, and ether was added followed by a saturated aqueous $Na_2S_2O_4$ solution. The aqueous solution was extracted with ether (4 times), and the organic phases were washed with a saturated aqueous $NaHCO_3$ solution and then with brine. The resulting solution was dried over $MgSO_4$, filtered, and evaporated, and the residue was purified by flash chromatography on silica gel (petroleum ether/AcOEt 4/1) to give **13** as a colorless oil (0.305 g, 80%). R_f = 0.33 (petroleum ether/EtOAc 4/1). $[\alpha]^{20}_D$ = +34.9 (c 0.8, CH_2Cl_2). IR (film): 3500, 1170, 1700, 1390, 1250, 1210, 1100 cm^{-1}. ^{1}H NMR: δ 7.39−7.18 (m, 10H), 4.74−4.62 (m, 1H), 4.54 (d, 1H, J = 12.1 Hz), 4.49 (d, 1H, J = 12.1 Hz), 4.30−4.20 (m, 1H), 4.15 (d_{app}, 2H, J = 4.8 Hz), 3.63−3.45 (m, 2H), 3.32 (dd, 1H, J = 13.4 and 3.1 Hz), 2.77 (dd, 1H, J = 13.4 and 9.7 Hz), 1.95−1.81 (m, 1H), 1.24 (d, 3H, J = 7.0 Hz), 1.10 (m, 1H), 0.88 (s, 9H), 0.85 (3H), 0.11 (s, 3H), 0.07 (s, 3H). ^{13}C NMR: δ 176.7, 153.1, 138.3, 135.3, 129.4, 128.9, 128.3, 2C), 127.5, 127.4, 127.3, 73.2, 73.0, 72.7, 72.2, 66.1, 55.5, 40.3, 38.4, 37.7, 28.8, 18.1, 10.9, 9.0, −4.4, −5.1. MS (CI^+, CH_4) m/z (rel intensity): 556 ($MH^{+\bullet}$, 100), 540 (18), 498 (17), 234 (38), 215 (18), 178 (15). HRMS (CI^+, CH_4): calcd for $C_{31}H_{46}NO_6Si$ ($MH^{+\bullet}$) 556.3098, found 556.3094.

(+)-(2*S*,3*R*,4*S*,5*R*)-6-Benzyloxy-5-(*tert*-butyldimethylsiloxy)-3-hydroxy-2,4-dimethyl-*N*-methoxy-*N*-methylhexanamide (14). To a suspension of *N*,*O*-dimethylhydroxylamine chlorhydrate (0.185 g, 1.89 mmol, 3 equiv) in CH_2Cl_2 (2.4 mL) at −15 °C was added a solution of $AlMe_3$ (0.946 mL, 2 M in toluene, 1.89 mmol, 3 equiv) at room temperature. After 30 min, the reaction media was cooled to −15 °C, and a solution of amide **13** (0.35 g, 0.631 mmol, 1 equiv) in CH_2Cl_2 (5.7 mL) was added. After 24 h at −15 °C, the reaction was quenched with a saturated aqueous potassium sodium tartrate solution and extracted with CH_2Cl_2 (4 times). The organic phases were dried over $MgSO_4$, filtered, and evaporated, and the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 1/1) to produce amide **14** as a colorless oil (0.269 g, 97%). R_f = 0.33 (petroleum ether/EtOAc 1/1). $[\alpha]^{20}_D$ = +8.7 (c 1.0, CH_2Cl_2). IR (film): 3440, 1640, 1460, 1250, 1100, 1060 cm^{-1}. ^{1}H NMR: δ 7.37−7.22 (m, 5H), 4.57 (d, 1H, J = 12.1 Hz), 4.46 (d, 1H, J = 12.1 Hz), 4.43 (ddd, 1H, J = 6.2, 6.2 and 1.6 Hz), 4.09 (d, 1H, J = 1.6 Hz, OH), 3.74 (ddd, 1H, J = 9.7, 2.2 and 1.6 Hz), 3.70 (s, 3H), 3.43 (d, 2H, J = 6.2 Hz), 3.21 (s, 3H), 3.09−2.95 (m, 1H), 1.78 (dqd, 1H, J = 9.7, 7.0 and 1.6 Hz), 1.15 (d, 3H, J = 7.0 Hz), 0.86 (s, 9H), 0.78 (d, 3H, J = 7.0 Hz), 0.09 (s, 3H), 0.05 (s, 3H). ^{13}C NMR: δ 138.5, 128.2, 127.6, 127.4, 72.9, 71.9, 69.6, 61.7, 37.6, 35.7, 25.9, 18.2, 9.4, 9.2, −4.3, −5.0. MS (EI, 70 eV) m/z (rel intensity): 424 ($[M - Me]^{+\bullet}$, 0.11), 382 (11), 300 (28), 274 (18), 173 (6), 117 (21), 91 (100), 75 (10). Anal. Calcd for $C_{23}H_{41}NO_5Si$: C, 62.83; H, 9.40; N, 3.19. Found: C, 62.43; H, 9.44; N, 3.04.

(+)-(2*S*,3*R*,4*S*,5*R*)-6-Benzyloxy-3,5-bis(*tert*-butyldimethylsiloxy)-2,4-dimethyl-*N*-methoxy-*N*-methylhexanamide (15). To a solution of amide **14** (0.271 g, 0.617 mmol, 1 equiv) in CH_2Cl_2 (8 mL) at −78 °C were added TBDMSOTf (0.426 mL, 1.85 mmol, 3 equiv) and 2,6-lutidine (0.430 mL, 3.70 mmol, 6 equiv). After 3 h at −40 °C, the reaction was quenched with a saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3 times). The organic phases were dried over $MgSO_4$, filtered, evaporated, and purified by silica gel chromatography (petroleum ether/EtOAc 9/1) to produce **15** as a colorless oil (0.33 mg, 97%). R_f = 0.25 (petroleum ether/EtOAc 9/1). $[\alpha]^{20}_D$ = −8.2 (c 1.55, CH_2Cl_2). IR (film): 1660, 1470, 1460, 1260, 1060 cm^{-1}. ^{1}H NMR: δ 7.36−7.22 (m, 5H), 4.56 (d, 1H, J = 11.9 Hz), 4.49 (d, 1H, J = 11.9 Hz), 4.05 (dd, 1H, J = 6.6 and 4.4 Hz), 3.69−3.61 (m, 1H), 3.66 (s, 3H), 3.53−3.46 (m, 2H), 3.14 (s, 3H), 3.09−2.96 (m, 1H), 1.91 (qdd, 1H, J = 7.2, 7.2 and 4.4 Hz), 1.12 (d, 3H, J = 7.0 Hz), 0.97 (d, 3H, J = 7.2 Hz), 0.90 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.01 (s, 3H). ^{13}C NMR: δ 173.7, 138.6, 128.1, 127.7, 127.5, 73.7, 73.5, 73.2, 72.8, 61.1, 42.7, 38.1, 26.1, 26.0, 18.4, 18.3, 14.1, 12.0, −3.8, −4.1, −4.4, −4.5. MS (EI, 70 eV) m/z (rel intensity): 538 ($[M - Me]^{+\bullet}$, 2), 496 (99), 300 (39), 260 (20), 204 (8), 149 (12), 117 (14), 91 (100), 73 (24). HRMS (CI^+, CH_4): calcd for $C_{29}H_{56}NO_5Si_2$ ($MH^{+\bullet}$) 554.3697, found

554.3705. Anal. Calcd for $C_{29}H_{55}NO_5Si_2$: C, 62.88; H, 10.01; N, 2.53. Found: C, 62.88; H, 10.07; N, 2.39.

(+)-(2*S*,3*R*,4*S*,5*R*)-6-Benzyloxy-3,5-bis(*tert*-butyldimethylsiloxy)-2,4-dimethylhexanal (16). To a solution of amide **15** (0.232 g, 0.419 mmol, 1 equiv) in THF (3.3 mL) at −78 °C was added a solution of DIBAL-H (0.503 mL, 1 M in hexane, 1.01 mmol, 2.4 equiv) dropwise. After 2 h at −78 °C, acetone was added to the reaction mixture, and 15 min after this addition, the reaction was poured on an aqueous solution of tartaric acid (0.5 M in H_2O, 28 mL) and cyclohexane (28 mL) and stirred for 1 h at room temperature. The aqueous phase was extracted with ether (5 times), the organic phases were dried over $MgSO_4$, filtered, and evaporated, and the residue was purified by flash chromatography on silica gel to produce aldehyde **16** as a colorless oil (0.184 g, 89%). R_f = 0.61 (petroleum ether/EtOAc 9/1). $[\alpha]^{20}_D$ = +21.5 (*c* 0.8, CH_2Cl_2). IR (film): 1725, 1470, 1460, 1250, 1100, 1030 cm^{-1}. ^1H NMR: δ 9.66 (s, 1H), 7.39−7.24 (m, 5H), 4.55 (d, 1H, *J* = 12.1 Hz), 4.47 (d, 1H, *J* = 12.1 Hz), 4.34 (dd, 1H, *J* = 6.9 and 2.1 Hz), 4.01 (dd, 1H, *J* = 5.5 and 3.6 Hz), 3.46 (dd, 1H, *J* = 9.6 and 5.5 Hz), 3.38 (dd, 1H, *J* = 9.6 and 5.5 Hz), 2.48 (qd, 1H, *J* = 7.0 and 2.1 Hz), 1.91 (qdd, 1H, *J* = 6.9, 6.9 and 3.6 Hz), 1.13 (d, 3H, *J* = 7.0 Hz), 0.89 (s, 9H), 0.88 (d, 3H, *J* = 6.9 Hz), 0.86 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H), −0.02 (s, 3H). ^{13}C NMR: δ 205.3, 138.2, 128.3, 127.6, 127.5, 73.5, 73.1, 72.0, 71.7, 49.8, 42.2, 26.0, 25.9, 18.4, 18.3, 10.6, −3.6, −4.0, −4.1, −4.4. MS (CI^+, CH_4) *m*/*z* (rel intensity): 512 ($[M + NH_4]^{+\bullet}$, 13), 437 (20), 353 (98), 305 (100), 265 (30), 255 (28), 215 (39), 185 (24). HRMS (CI^+, CH_4): calcd for $C_{27}H_{54}NO_4Si_2$ $[M + NH_4]^{+\bullet}$ 512.3591, found 512.3585.

(+)-(2*S*,3*R*,4*S*,5*R*)-5-Benzyloxy-2,4-bis(*tert*-butyldimethylsiloxy)-1,3-dimethylpentyl]-1,3-dithiane (17). To a solution of aldehyde **16** (0.182 g, 0.368 mmol, 1 equiv) in CH_2Cl_2 (14 mL) at −78 °C was added 1,3-propanedithiol (0.186 mL, 1.84 mmol, 5 equiv) followed by a dropwise addition of $TiCl_4$ (80 μL, 0.74 mmol, 2 equiv). After 30 min at −78 °C, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution and warmed to room temperature. The aqueous phase was extracted with CH_2Cl_2 (5 times), the organic phases were dried over $MgSO_4$, filtered, and evaporated, and the residue was purified by flash chromatography on silica gel (petroleum ether, AcOEt 95/5) to give thioketal **17** as a white oil (0.211 g, 98%). R_f = 0.50 (petroleum ether/EtOAc 95/5). $[\alpha]^{20}_D$ = +1.4 (*c* 2.5, CH_2Cl_2). IR (film): 1460, 1250, 1085, 1030 cm^{-1}. ^1H NMR: δ 7.39−7.24 (m, 5H), 4.56 (d, 1H, *J* = 12.1 Hz), 4.46 (d, 1H, *J* = 12.1 Hz), 4.20 (dd, 1H, *J* = 6.6 and 2.2 Hz), 4.02−3.94 (m, 1H), 3.98 (d, 1H, *J* = 9.2 Hz), 3.48 (dd, 1H, *J* = 10.0 and 5.9 Hz), 3.41 (dd, 1H, *J* = 10.0 and 4.4 Hz), 2.92−2.68 (m, 4H), 2.14−2.02 (m, 1H), 1.99−1.77 (m, 3H), 1.05 (d, 3H, *J* = 6.6 Hz), 0.91 (s, 9H), 0.88 (s, 9H), 0.85 (d, 3H, *J* = 7.3 Hz), 0.14 (s, 6H), 0.10 (s, 3H), 0.05 (s, 3H). ^{13}C NMR: δ 138.4, 128.2, 127.6, 127.4, 73.9, 73.1, 72.8, 72.2, 52.3, 41.8, 40.1, 30.3, 30.2, 26.2, 26.1, 26.0, 18.6, 18.4, 11.7, 11.2, −3.5, −3.6, −4.3. MS (CI^+, CH_4) *m*/*z* (rel intensity): 585 ($MH^{+\bullet}$, 12), 569 (37), 527 (48), 487 (9), 435 (100), 437 (13). HRMS (CI^+, CH_4): calcd for $C_{30}H_{57}O_3S_2Si_2$ ($MH^{+\bullet}$) 585.3288, found 585.3272.

(−)-(3*S*,4*R*,5*S*,6*R*)-6-Benzyloxymethyl-4-hydroxy-3,5-dimethyltetrahydropyran-2-one (18). To a solution of **14** (0.06 g, 0.14 mmol, 1 equiv) in THF (2.4 mL) at 0 °C was added a solution of HF·pyr complex (0.70 mL). After 5 min at room temperature, the reaction mixture was diluted with Et_2O and H_2O, and Na_2CO_3 (solid) was added in small portions until pH = 7−8 was obtained. The aqueous phase was extracted with Et_2O (5 times), and the organic phases were dried over $MgSO_4$, filtered, evaporated, and purified by flash chromatography on silica gel to produce **18** as a colorless oil (0.028 g, 77%). R_f = 0.30 (petroleum ether/EtOAc 1/1). $[\alpha]^{20}_D$ = −59.5 (*c* 1.15, CH_2Cl_2). IR (film): 1720, 1450, 1370, 1360, 1210, 1100, 1050 cm^{-1}. ^1H NMR: δ 7.42−7.28 (m, 5H), 4.62 (d, 1H, *J* = 11.9 Hz), 4.57 (d, 1H, *J* = 11.9 Hz), 4.48 (ddd, 1H, *J* = 5.6, 4.9 and 3.9 Hz), 3.82−3.70 (m, 1H), 3.71 (dd, 1H, *J* = 10.1 and 4.9 Hz), 3.63 (dd, 1H, *J* = 10.1 and 5.6 Hz), 2.66 (bd, 1H, OH), 2.58 (qd, 1H, *J* = 7.3 and 7.3 Hz), 2.40 (qdd, 1H, *J* = 7.2, 4.0 and 3.9 Hz), 1.39 (d, 3H, *J* = 7.3 Hz), 0.99 (d, 3H, *J* = 7.2 Hz). ^{13}C NMR: δ 173.1, 137.0, 128.6, 128.1, 127.9, 78.6, 73.9, 73.1, 68.6, 41.3, 34.2, 15.4, 6.7. MS (CI^+, CH_4) *m*/*z* (rel intensity): 265 ($MH^{+\bullet}$, 100), 247 (8), 185 (12), 157 (27), 139 (19), 125 (23), 119 (16). HRMS (CI^+, CH_4): calcd for $C_{15}H_{21}O_4$ ($MH^{+\bullet}$) 265.1440, found 265.1437.

1-Benzyloxy-3,5-dimethyl-hexane-2,4-diols (19) and (19′). To a solution of β-hydroxyketones **8** and **8′** (0.639 g, 2.56 mmol, 1 equiv) in acetic acid (8.5 mL) at 0 °C was added dropwise a solution of $Me_4NBH(OAc)_3$ (2.03 g, 7.68 mmol, 3 equiv) in AcOH (17 mL). After 12 h at room temperature, CH_2Cl_2 (32 mL) was added to the reaction mixture, and then a saturated aqueous $NaHCO_3$ solution (32 mL) was slowly added. After 45 min at room temperature, the aqueous phase was extracted with CH_2Cl_2 (3 times), then the organic phases were dried over $MgSO_4$, filtered, and evaporated, and the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 2/1) to produce an inseparable mixture of two diastereomers **19** and **19′** as (0.49 g, dr = 90/10, 76%). R_f = 0.24 (petroleum ether/EtOAc 2/1). IR (film): 3490, 1450, 1090 cm^{-1}. ^1H NMR: δ 7.41−7.28 (m, 5H), 4.61 (d, 1H, *J* = 11.8 Hz), 4.55 (d, 1H, *J* = 11.8 Hz), 4.24−4.15 (m, 1H), 3.57 (dd, 1H, *J* = 9.5 and 8.1 Hz), 3.50 (dd, 1H, *J* = 9.5 and 3.8 Hz), 3.30 (t_{app}, 1H, *J* = 6.1 Hz), 2.99 (bs, 1H, OH), 2.89 (bs, 1H, OH), 2.00−1.75 (m, 2H), 0.95 (d, 3H, *J* = 6.6 Hz), 0.94 (d, 3H, *J* = 7.4 Hz), 0.92 (d, 3H, *J* = 6.6 Hz). ^{13}C NMR: δ 138.0, 128.5, 127.8, 127.7, 80.2, 73.5, 72.5, 71.5, 36.4, 30.8, 19.7, 16.7, 11.9. MS (EI, 70 eV) *m*/*z* (rel intensity): 161 ($[M - PhCH_2]^{+\bullet}$, 2), 131 (13), 107 (17), 101 (7), 91 (100), 73 (21).

(−)-(4*S*,5*R*,6*R*)-4-Benzyloxymethyl-6-isopropyl-2,2,5-trimethyl-1,3-dioxane (20). Into the diastereomeric mixture of **19** and **19′** (0.3 g, 1.19 mmol, 1 equiv) in acetone (4.2 mL) were added 2,2-dimethoxypropane (1.46 mL, 11.9 mmol, 10 equiv) and CSA (5 mol %). After 5 h at room temperature, the reaction mixture was concentrated under vacuum, and the residue was purified by flash chromatography on silica gel (petroleum ether/CH_2CL_2 8/2). Ketal **20** was obtained as a white solid (0.231 g, 67%). R_f = 0.43 (petroleum ether/CH_2Cl_2 8/2). $[\alpha]^{20}_D$ = −21.0 (*c* 1.0, CH_2Cl_2). Mp: 54 °C. IR (film): 1450, 1375, 1220, 1100, 1025 cm^{-1}. ^1H NMR: δ 7.38−7.33 (m, 5H), 4.64 (d, 1H, *J* = 11.9 Hz), 4.50 (d, 1H, *J* = 11.9 Hz), 4.07 (ddd, 1H, *J* = 7.0, 5.8 and 4.6 Hz), 3.51 (dd, 1H, *J* = 9.7 and 7.0 Hz), 3.46 (dd, 1H, *J* = 9.7 and 5.8 Hz), 3.06 (dd, 1H, *J* = 7.3 and 5.1 Hz), 1.86 (m, 1H), 1.73 (m, 1H), 1.37 (s, 3H), 1.35 (s, 3H), 0.95 (d, 3H, *J* = 6.8 Hz), 0.93 (d, 3H, *J* = 6.8 Hz), 0.85 (d, 3H, *J* = 6.9 Hz). ^{13}C NMR: δ 138.4, 128.3, 127.7, 127.5, 100.4, 79.1, 73.3, 69.9, 68.4, 35.2, 31.6, 25.4, 23.5, 18.7, 17.5, 12.5. MS (EI, 70 eV) *m*/*z* (rel intensity): 292 ($MH^{+\bullet}$, 0.02), 277 (7), 171 (8), 162 (8), 118 (12), 107 (19), 91 (100), 69 (12), 59 (12). Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.92; H, 9.74.

(−)-(4*S*,5*R*,6*S*)-4-Benzyloxymethyl-6-isopropyl-2,2,5-trimethyl-1,3-dioxane (20′). ^1H NMR: δ 7.15−7.30 (m, 5H), 4.58 (d, 1H, *J* = 12.1 Hz), 4.43 (d, 1H, *J* = 12.1 Hz), 4.05 (ddd, 1H, *J* = 6.3, 6.3 and 2.6 Hz), 3.44 (dd, 1H, *J* = 9.6 and 6.6 Hz), 3.37 (dd, 1H, *J* = 9.7 and 5.8 Hz), 3.26 (dd, 1H, *J* = 9.6 and 5.9 Hz), 1.50−1.65 (m, 2H), 1.35 (d, 3H, *J* = 4.5 Hz), 1.20 (s, 6H), 0.89 (d, 3H, *J* = 6.6 Hz), 0.72 (d, 3H, *J* = 6.6 Hz). ^{13}C NMR: δ 128.2, 127.7, 127.5, 78.9, 73.3, 72.3, 71.0, 30.8, 29.8, 29.0, 19.6, 19.5 (2C), 17.3.

(2*S*,3*R*,4*R*)-1-Benzyloxy-2,4-bis(*tert*-butyldimethylsiloxy)-3,5-dimethylhexane (21). To a solution of diols **19** and **19′** (0.118 g, 0.468 mmol, 1 equiv) in CH_2Cl_2 (6 mL) at −78 °C were added TBDMSOTf (0.323 mL, 1.40 mmol, 3 equiv) and 2,6-lutidine (0.326 mL, 2.81 mmol, 6 equiv). After 1 h at −78 °C and 2 h at −35 °C, the reaction was quenched with a saturated aqueous NH_4Cl solution. The aqueous phase was extracted with CH_2Cl_2 (4 times). The organic phases were dried over $MgSO_4$, filtered, and evaporated, and the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 9/1) to give **21** as a colorless oil (0.202 g, 90%).

R_f = 0.90 (petroleum ether/EtOAc 9/1). $[\alpha]^{20}_D$ = 0.0 (*c* 1.05, CH_2Cl_2). IR (film): 1465, 1255, 1050 cm^{-1}. ^1H NMR: δ 7.36−7.25 (m, 5H), 4.54 (d, 1H, *J* = 11.8 Hz), 4.48 (d, 1H, *J* = 11.8 Hz), 3.99−3.92 (m, 1H), 3.50 (dd, 1H, *J* = 6.2 and 2.9 Hz), 3.45 − 3.42 (m, 2H), 1.87−1.72 (m, 2H), 0.91 (s, 9H), 0.90−0.86 (6H), 0.87 (s, 9H), 0.85 (d, 3H, *J* = 7.0 Hz), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR: δ 138.5, 128.2, 127.6, 127.4, 78.4, 74.6, 73.1, 72.8, 41.2, 30.7, 26.2, 25.7, 25.6, 21.5, 18.5, 18.4, 16.7, 11.6, −3.6, −3.4, −4.0, −4.4. MS (CI^+, CH_4) *m*/*z* (rel intensity): 481 ($MH^{+\bullet}$, 23), 465 (21), 423 (34), 373 (42), 357 (36), 349 (46), 315 (74), 257 (21), 241 (54), 217 (44), 187 (100). HRMS (CI^+, CH_4): calcd for $C_{27}H_{53}O_3Si_2$ ($MH^{+\bullet}$) 481.3533, found 481.3527.

(+)-(2*S*,3*R*,4*R*)-2,4-Bis(*tert*-butyldimethylsiloxy)-3,5-dimethylhexan-l-ol (22). A solution of **21** (0.230 g, 0.479 mmol, 1 equiv), K_2CO_3 (0.05 g), Pd/C 10% (0.05 g, 4.8.0 μmol, 0.1 equiv) was stirred under 1 atm of hydrogen at room temperature. After 2 h, the reaction was filtered through Celite, and the filtrate was evaporated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 95/5) to give alcohol **22** as a colorless oil (0.133 g, 71%). R_f = 0.45 (petroleum ether/EtOAc 95/5). $[\alpha]^{20}_D$ = +2.7 (*c* 1.55, CH_2Cl_2). IR (film): 3450, 1460, 1390, 1360, 1255, 1040 cm^{-1}. ^1H NMR: δ 3.73−3.65 (m, 1H), 3.67−3.55 (m, 2H), 3.41 (dd, 1H, *J* = 4.6 and 4.6 Hz), 2.04 (dd, 1H, *J* = 7.9 and 4.6 Hz, OH), 1.94 (qdd, 1H, *J* = 7.3, 7.3 and 4.6 Hz), 1.81 (dqd, 1H, *J* = 6.9, 6.9 and 4.6 Hz), 0.95 (d, 3H, *J* = 7.0 Hz), 0.93 (s, 9H), 0.92 (3H), 0.91 (s, 9H), 0.89 (d, 3H, *J* = 6.6 Hz), 0.1 (s, 6H), 0.09 (s, 3H), 0.07 (s, 3H). ^{13}C NMR: δ 79.4, 74.6, 65.3, 40.2, 31.7, 26.1, 25.9, 21.0, 18.4, 18.2, 18.1, 14.5, −3.6, −4.2, −4.3, −4.4. MS (CI^+, CH_4) *m*/*z* (rel intensity): 391 ($MH^{+\bullet}$, 53), 333 (41), 259 (100), 243 (43), 175 (19), 127 (14). HRMS (CI^+, CH_4): calcd for $C_{20}H_{47}O_3Si_2$ ($MH^{+\bullet}$) 391.3070, found 391.3065.

(−)-(2*S*,3*R*,4*R*)-2,4-Bis(*tert*-butyldimethylsiloxy)-1-iodo-3,5-dimethylhexane (23). To a solution of **22** (0.067 g, 0.17 mmol, 1 equiv), imidazole (0.023 g, 0.34 mmol, 2 equiv), and PPh_3 (0.091 g, 0.34 mmol, 2 equiv) in toluene (0.7 mL) at 0 °C was added. After 1.5 h, I_2 (0.088 g, 0.34 mmol, 2 equiv), Et_2O, and H_2O were added to the reaction mixture at 0 °C. The aqueous phase was extracted with Et_2O (3 times). The organic phases were dried over $MgSO_4$, filtered, and evaporated, and the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 92/2) to give iodide **23** as a yellow oil (0.082 g, 95%). R_f = 0.74 (petroleum ether/EtOAc 98/2). $[\alpha]^{20}_D$ = −9.5 (*c* 1.5, $CHCl_3$). IR (film): 1465, 1250, 1050 cm^{-1}. ^1H NMR: δ 3.43−3.23 (m, 4H), 2.03−1.90 (m, 1H), 1.76 (qqd, 1H, *J* = 6.7, 6.7 and 3.5 Hz), 0.94 (d, 3H, *J* = 6.7 Hz), 0.93 (s, 9H), 0.92 (s, 9H), 0.92 (d, 3H, *J* = 7.0 Hz), 0.89 (d, 3H, *J* = 6.7 Hz), 0.13 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H). ^{13}C NMR: δ 78.4, 71.6, 42.9, 31.3, 26.1, 25.9, 21.4, 18.4, 18.2, 17.3, 15.4, 12.2, −3.3, −3.8, −4.2. MS (CI^+, CH_4) *m*/*z* (rel intensity): 501 ($MH^{+\bullet}$, 15), 485 (14), 443 (15), 369 (53), 303 (15), 285 (18), 241 (90), 237 (100), 187 (49), 109 (22). HRMS (CI^+, CH_4): calcd for $C_{20}H_{46}O_2ISi_2$ ($MH^{+\bullet}$) 501.2081, found 501.2083.

(−)-2-(1*S*,2*R*,3*S*,4*R*)-5-Benzyloxy-2,4-bis[(*tert*-butyldimethylsiloxy)-1,3-dimethylpentyl]-2-(2*R*,3*S*,4*R*)-2,4-bis-[(*tert*-butyldimethylsiloxy)-3,5-dimethylhexyl]-1,3-dithiane (24). To a solution of thioketal **17** (0.062 g, 0.106 mmol, 1 equiv) in THF (0.5 mL) at −78 °C were added HMPA (74 mL, 0.43 mmol, 4.02 equiv) and *t*-BuLi (1.7 M in pentane) until the yellow color became persistent, at which time an extra addition of *t*-BuLi (75 mL, 1.7 M in pentane, 0.13 mmol, 1,2 equiv) was made. After 1 h at −78 °C, a solution of iodide **23** (0.07 g, 0.14 mmol, 1.33 equiv) in THF (0.3 mL) was added. The reaction was quenched 1 h later at −78 °C with a saturated aqueous NH_4Cl solution and extracted with EtOAc (3 times). The organic phases were dried over $MgSO_4$, filtered, and evaporated, and the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 95/5) and then on TLC plates (same eluant) to give **24** as a colorless oil (0.028 g, 28%). R_f = 0.24 (petroleum ether). $[\alpha]^{20}_D$ = −1.5 (*c* 0.75, CH_2Cl_2). IR (film): 1470, 1460, 1390, 1360, 1255, 1070 cm^{-1}. ^1H NMR: δ 7.35−7.25 (m, 5H), 4.56 (d, 1H, *J* = 11.9 Hz), 4.45 (d, 1H, *J* = 11.9 Hz), 4.32 (d_{app}, 1H, *J* = 7.5 Hz), 4.16−4.11 (m, 1H), 3.79−3.55 (m, 4H), 2.95−2.38 (m, 5H), 2.12 (dd, 1H, *J* = 15.9 and 7.5 Hz), 2.06−1.70 (m, 4H), 1.49 (d, 1H, *J* = 15.9 Hz), 1.31−1.24 (m, 1H), 1.06 (d, 3H, *J* = 6.6 Hz), 1.02 (d, 3H, *J* = 6.6 Hz), 0.97−0.88 (m, 45H), 0.26−0.04 (m, 24H). ^{13}C NMR: δ 139.0, 128.6, 128.2, 127.8, 79.2, 74.7, 73.8, 73.6, 71.9, 70.5, 59.5, 48.7, 44.7, 43.1, 39.9, 30.4, 27.3, 26.6, 26.6, 26.6, 26.5, 26.4, 25.8, 24.3, 22.6, 19.1, 18.9, 18.6, 17.2, 13.0, 12.4, 8.2, −1.4, −2.7, −2.8, −3.3, −3.6, −3.9, −3.9, −4.0. MS (CI^+, CH_4) *m*/*z*: 957 ($MH^{+\bullet}$, 4), 941 (9), 825 (19), 693 (12), 437 (68), 305 (57), 187 (100), 185 (16). HRMS (CI^+, CH_4): calcd for $C_{50}H_{101}O_5S_2Si_4$ ($MH^{+\bullet}$) 957.6168, found 957.6143.

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