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Novel Synthesis of Highly Functionalized 14-β-Hydroxysteroids Related to Batrachotoxin and Ouabain

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The use of anionic polycyclization was investigated in an effort to develop a versatile and convergent synthesis of advanced tetracyclic intermediates of batrachotoxin and ouabain analogues. Two new 5-(trialkylsilyl)-2-cyclohexenones as A ring precursors and a new Nazarov intermediate (D ring precursor) were prepared for this purpose. The reaction of the unsaturated β-keto aldehyde A ring precursor with the enolate of the Nazarov intermediate afforded, after subsequent transformations, a 14-β-hydroxysteroid with complete control of stereochemistry.

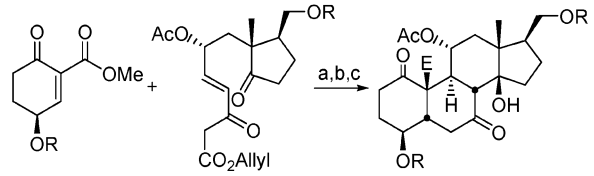
Introduction

We recently reported the use of anionic polycyclization for constructing the steroidal backbone of the cardenolides. It was shown that the reaction of 2-carbomethoxy-2-cyclohexenone (−)-**5** with the enolate of Nazarov intermediate (−)-**6** gave, after decarboxylation and aldol condensation, steroid (−)-**7** with control of stereochemistry (Scheme 1).[1] With the stereoselective generation of five contiguous chiral centers, the crucial groundwork was established for the asymmetric total synthesis of interesting natural products such as ouabain. To pursue this line of research, we then focused our attention on investigating other A ring cyclohexenones and another D ring precursor. This strategy was intended to synthesize an advanced intermediate of batrachotoxin (**4**) and analogues of ouabain (**2**) (Figure 1).[2] Batrachotoxin is one of the most potent known cardiotoxins (LD_{50} in mice = 2 μg/kg). This molecule acts by binding to sites in nerve and muscle cells associated with sodium ion transport channels. The binding prevents closure of the channel allowing a massive influx of sodium ions to flow into the cell leading to membrane depolarization.[3] In this paper, we wish to report the synthesis of two new A ring cyclohexenones ((+)-**10** and (+)-**12**) having a dimethylphenylsilyl group at C(3) (steroid numbering) for stereocontrol and a new Nazarov intermediate (D ring precursor (−)-**29**) and the results of anionic polycyclization with both cyclohexenones.

Results and Discussion

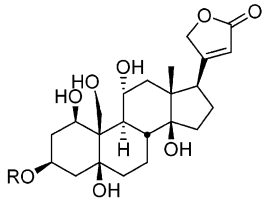
Previous studies in our group used unsaturated β-keto ester as A ring precursors which were allowed to react in a cycloaddition reaction[4] with a Nazarov intermediate to afford after subsequent steps a tetracyclic compound with an ester at the C(10) position (Scheme 1).[1,5] In many of our planned synthetic routes, these esters would need

SCHEME 1[a]

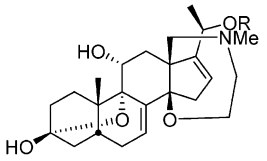


(-)-5 (-)-6 (-)-7

[a] Reagents and conditions: (a) Cs_2CO_3, CH_2Cl_2, 61%; (b) $Pd(PPh_3)_4$, morpholine, THF, 71%; (c) KHMDS, THF reflux, 71%. E = CO_2Me; R = TBDPS.



1 Ouabagenin (R = H)
2 Ouabain (R = alpha-(L)-Rhamnosyl)



3 Batrachotoxinin A (R = H)
4 Batrachotoxin (R = 3-CO-2,4-dimethylpyrrole)

FIGURE 1. Target structures.

(1) Yang, Z.; Shannon, D.; Truong, V.-L.; Deslongchamps, P. *Org. Lett.* **2002**, *4*, 4693.

(2) For a total synthesis of batrachotoxinin A, see: Kurosu, M.; Marcin, L. R.; Grinsteiner, T. J.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 6627.

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(4) This cycloaddition process can be looked as a double Michael addition or a highly desymmetrized Diels−Alder reaction.

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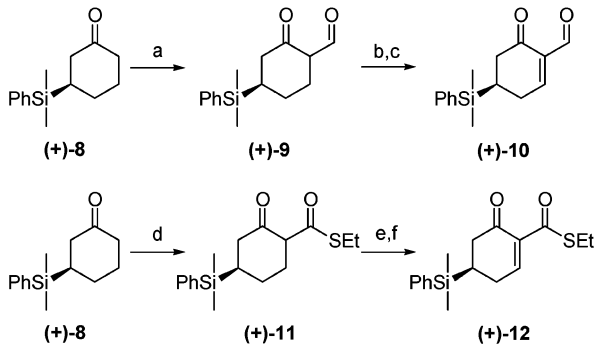
SCHEME 2[a]



[a] Reagents and conditions: (a) (i) KH, THF, (ii) HCO_2Et, 84%; (b) PhSeCl, pyridine, CH_2Cl_2, 88%; (c) H_2O_2, CH_2Cl_2, quant.; (d) (i) $(TMS)_2NH$, *n*-BuLi, THF, −78 °C, (ii) ClCOSEt, 72%; (e) PhSeCl, pyridine, CH_2Cl_2, 83%; (f) H_2O_2, CH_2Cl_2, 97%.

to be reduced to the corresponding alcohols or alkanes. This step could be problematic since there are other carbonyl functionalities in these compounds. We then decided to investigate the use of unsaturated β-keto aldehydes and β-keto thioesters (a masked β-keto aldehyde) as A ring precursors. Furthermore, a couple of years ago, Corey and co-workers reported the facile synthesis of enantiomerically pure 5-(trialkylsilyl)-2-cyclohexenones where the silyl group was used as a stereocontrolling group in Diels−Alder reaction.[6,7] With this in mind, the synthesis of unsaturated β-keto aldehyde (+)-**10** was then undertaken starting from ketone (+)-**8**[6] (Scheme 2). Kinetic deprotonation of ketone (+)-**8** with potassium hydride gave, after addition of ethyl formate, β-keto aldehyde (+)-**9** in 84% yield. The introduction of the unsaturation was accomplished by formation of the selenide derivative with PhSeCl and pyridine in CH_2Cl_2. Treatment of the selenide derivative with H_2O_2 gave the unsaturated β-keto aldehyde (+)-**10** in 88% yield for the last two steps. In the same fashion, unsaturated β-keto thioester (+)-**12** was prepared by deprotonation of ketone (+)-**8** with LiHMDS and trapping of the kinetic enolate with ethyl chlorothiolformate, formation of the selenide with PhSeCl and pyridine, and oxidation with H_2O_2 in a three-step sequence with an overall yield of 58%.

We then investigated the synthesis of the Nazarov intermediate bearing an ester at C(13) (steroid numbering). An ester functionality at this position was as yet unexplored in the anionic polycyclization strategy. This ester would also provide a handle for facile access to the E ring of batrachotoxin. The synthesis of Nazarov intermediate (−)-**29** started from the previously reported cyclopropane **17** (Scheme 3).[8] The latter was made by coupling of the dianion of methyl acetoacetate (**14**) and 1-bromo-2-butyne (**13**), partial hydrogenation with Lindlar's catalyst,[9] and cyclization after formation of the carbene via the iodonium ylide moiety.[10,11] With racemic **17** in hand, opening of the cyclopropane was carried out with $Mg(OMe)_2$ in refluxing methanol to afford β-keto ester **18**.[12] Next, we used chiral auxiliary (*R*)-(−)-pantolactone ((−)-**40**) to execute a transesterification using Taber's methodology.[13] In a recent publication, Covey and co-workers reported the use of (*R*)-(−)-pantolactone ((−)-**40**) as a good chiral auxiliary to separate diastereoisomers of compounds similar to β-keto ester **18**.[14] In our case, it also gave good results; the lactone diastereoisomers (+)-**19** and (−)-**20** were easily separated by flash chromatography. Identification of diastereoisomer (−)-**20** was performed by single-crystal X-ray diffraction crystallography.[15] After methanolysis, we obtained enantiopure β-keto ester (−)-**18**.

The construction of the backbone of the Nazarov intermediate began with the addition of methyl vinyl ketone to β-keto ester (−)-**18** under basic conditions (K_2CO_3 in benzene at room temperature) to afford methyl ketone (−)-**22** in 92% yield. Cyclization of the latter with pyrrolidine in refluxing benzene gave the enamine, which was hydrolyzed with a heterogeneous mixture of buffered aqueous solution and benzene to afford enone (+)-**23** in 70% yield.[16] Following the method previously developed in our laboratory, the enone (+)-**23** was transformed into compound (−)-**29**.[1] Introduction of the acetate was made with lead tetraacetate in toluene in a high-pressure tube. Heating of the mixture at 150 °C for a prolonged time permitted thermodynamic equilibration and gave the α-acetoxy ketone (+)-**24** in 72% yield in a >20:1 ratio of diastereoisomers. The enone of acetate (+)-**24** was cleaved to afford carboxylic acid (−)-**25** in 74% yield. Thioesterification of the acid with DCC, DMAP, and ethanethiol in dichloromethane furnished thioester (−)-**26**. Homologation of the latter was accomplished by reduction of the thioester with Et_3SiH and $Pd(OAc)_2$ to give aldehyde (−)-**27**, which was immediately treated with phosphorane **39** to afford enol ether (−)-**28** in 80% yield for both steps.[17] Final deprotection of the enol ether in 80% aqueous acetic acid at 80 °C provided Nazarov intermediate (−)-**29** in 74% yield.

The cycloaddition reaction could now be performed on both A ring cyclohexenones. The Nazarov intermediate (−)-**29** was allowed to react with unsaturated β-keto thioester (+)-**12** (Scheme 4). Under standard conditions (Cs_2CO_3 in CH_2Cl_2), cycloaddition gave poor results. We only managed to obtain a 16% yield of tricycle **30** as indicated by its NMR spectrum. Decomposition of the β-keto thioester starting material seemed to be the major problem. Nonetheless, decarboxylation of the allyl ester with $Pd(PPh_3)_4$ and morpholine in THF yielded tricycle

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(15) We thank Mr. Andreas Decken for the X-ray diffraction analysis.
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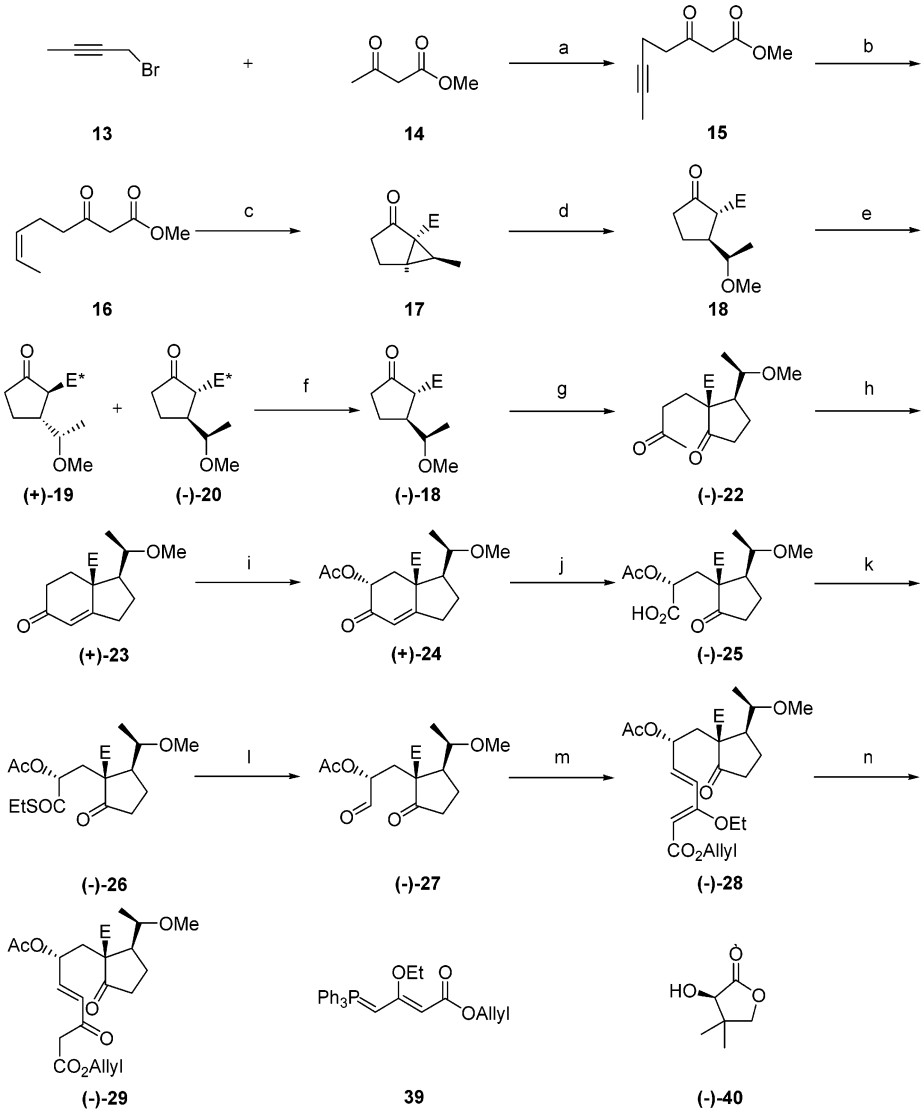
(17) Dubé, P.; Chapdelaine, D.; Deslongchamps, P. *Synlett* **2000**, 1819.

SCHEME 3[a]

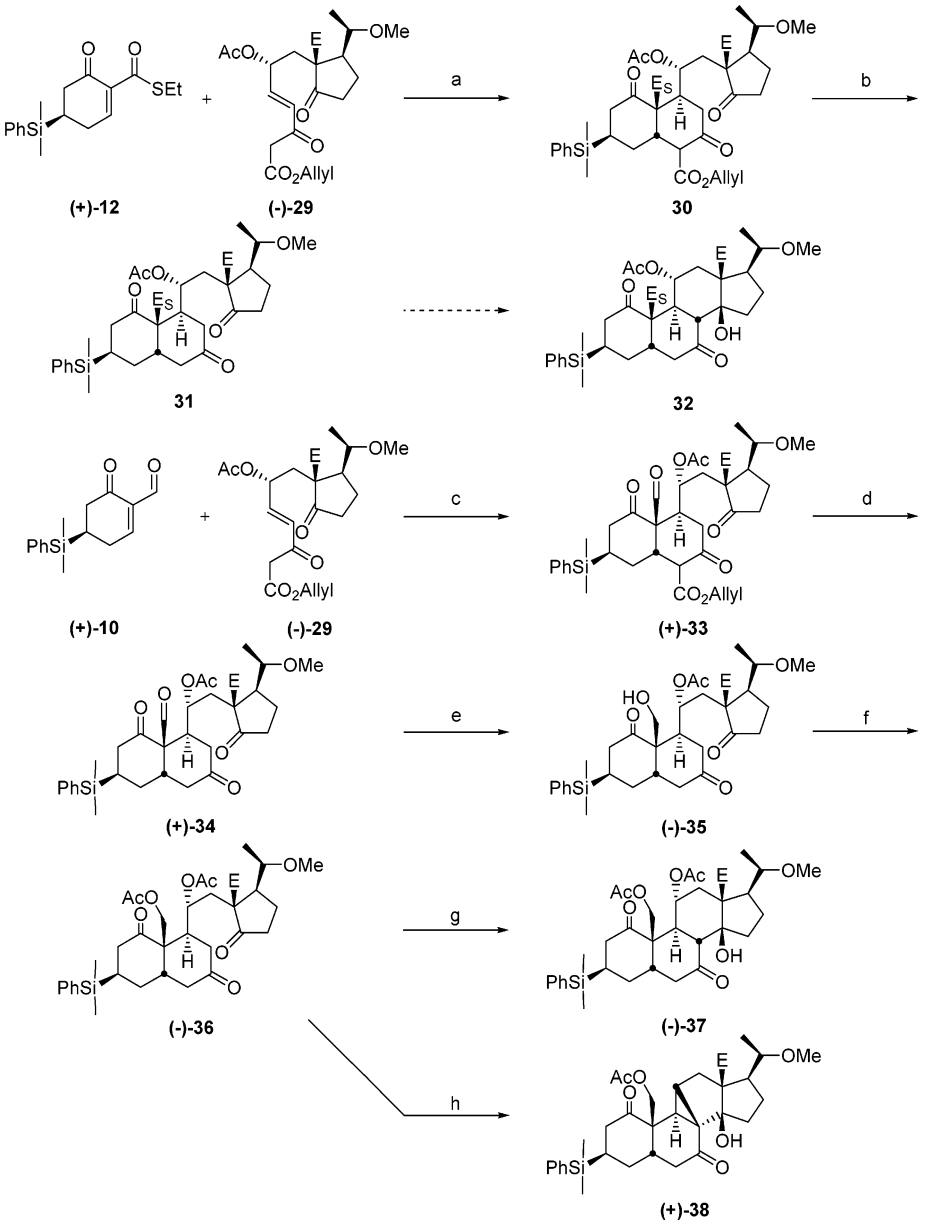


[a] Reagents and conditions: (a) (i) NaH, THF 0 °C, (ii) *n*-BuLi, 77%; (b) Lindlar's cat., H_2, Et_2O, 95%; (c) (i) KOH, $PhI(OAc)_2$, MeOH, 0 °C, (ii) *hν*, 60%; (d) Mg, MeOH reflux, 74%; (e) (*R*)-(−)-pantolactone ((−)-**40**), DMAP, toluene reflux, 75% (ratio of (+)-**19**/(−)-**20** = 1/1); (f) sealed tube, MeOH, 105 °C, 95%; (g) methyl vinyl ketone, K_2CO_3, benzene, 92%; (h) (i) pyrrolidine, benzene reflux, (ii) NaOAc, AcOH, H_2O, benzene reflux, 70%; (i) $Pb(OAc)_4$, sealed tube, toluene 150 °C, 72%; (j) $NaIO_4$, $RuCl_3$, H_2O, MeCN, $CHCl_3$, 74%; (k) EtSH, DCC, DMAP, CH_2Cl_2, 73%; (l) Et_3SiH, $Pd(OAc)_2$, acetone; (m) phosphorane **39**, benzene reflux, 80% (two steps); (n) AcOH, H_2O, 80 °C, 74%. E = CO_2Me; E* = CO_2-*β*,*β*′-dimethyl-*γ*-butyrolactone.

31. Unfortunately, the subsequent aldol reaction was not successfully accomplished with this tricycle. We then turned our attention to unsaturated *β*-keto aldehyde (+)-**10** as an A ring precursor. Cycloaddition with Nazarov intermediate (−)-**29** went very smoothly to afford allyl ester (+)-**33** in excellent yield (97%). Interestingly, we observed only one product from the cyclization. We concluded that the silyl group at the C(3) position very efficiently controlled the stereoselectivity of the cycloaddition reaction. Due to these results, the thioester approach was not further investigated as it was only intended to be used as a masked aldehyde.

Decarboxylation of the allyl ester was then performed with $Pd(PPh_3)_4$ and morpholine in THF to give rise to tricycle (+)-**34** in 62% yield. We had to be very careful with the amount of morpholine used in this reaction because the aldehyde at the C(10) position was prone to deformylation. Next, we decided to selectively reduce the aldehyde with lithium tris[(3-ethyl-3-pentyl)oxy]-aluminohydride at −45 °C to afford alcohol (−)-**35**, which was protected as an acetate with acetic anhydride and DMAP in pyridine. The next step was the aldol condensation. Initially, the reaction was carried out with KHMDS in refluxing THF to obtain tetracycle (−)-**37** in an unoptimized yield of 35% with complete control of stereochemistry. Compound (−)-**37** is assumed to have the H(8) *β*-configuration as in previous related cases.[1] This tetracycle could be looked at as an advanced intermediate of batrachotoxin or as precursors of ouabain analogues. Finally, we also tried Cs_2CO_3 in refluxing acetonitrile for 16 h and it afforded cyclopropane (+)-**38** in an unoptimized yield of 38%. The structure and stereochemistry of cyclopropane (+)-**38** was confirmed by single-crystal X-ray diffraction crystallography.[15] Pre-

SCHEME 4[a]



[a] Reagents and conditions: (a) Cs_2CO_3, CH_2Cl_2, 16%; (b) $Pd(PPh_3)_4$, morpholine, THF, 81%; (c) Cs_2CO_3, CH_2Cl_2, 97%; (d) $Pd(PPh_3)_4$, morpholine, THF, 62%; (e) $LiAl(OCEt_3)_3H$, THF, −45 °C, 72%; (f) Ac_2O, DMAP, pyridine, 94%; (g) KHMDS, THF reflux, 35%; (h) Cs_2CO_3, MeCN reflux, 38%. E = CO_2Me; E_S = COSEt.

sumably, the long reaction time in refluxing acetonitrile allowed the formation of the cyclopropane via an additional deprotonation at C(8) on compound (−)-**37** followed by displacement of the acetate at C(11) by the resulting enolate.

Conclusion

We have elaborated an efficient stereocontrolled route for the synthesis of a tetracyclic precursor to batrachotoxin and analogues of ouabain. The use of 5-(trialkylsilyl)-2-cyclohexenones controlled in a very efficient manner the stereoselectivity of the cycloaddition reaction. Furthermore, the aldehyde group on the A ring cyclohexenone afforded a very good yield for the cycloaddition step and permitted facile, selective transformation without perturbing other functionalities. Current efforts in our laboratories are now directed at the optimization of the last steps in the sequence to produce more advanced intermediates. Developments regarding these efforts will be reported in due time.

Experimental Section

All reactions were performed under nitrogen atmosphere with flame-dried glassware. Solvents were distilled and dried according to standard procedures. ^1H and ^{13}C NMR spectra are referenced with respect to the residual signals of the solvent; they are described with standard abbreviations. Melting points are uncorrected.

***β*-Keto Aldehyde (+)-9.** Potassium hydride (35 wt % dispersion in mineral oil) was rinsed three times with pentane to afford pure material (0.072 g, 1.8 mmol), which was

suspended in THF (5.0 mL). This solution was then cooled to 0 °C. A solution of ketone (+)-**8** (0.38 g, 1.6 mmol) in THF (6.0 mL) was added to the first solution dropwise. The reaction mixture was stirred for 0.5 h at room temperature and cooled to 0 °C. Ethyl formate (0.27 mL, 3.3 mmol) was added and the mixture was stirred for 0.5 h at room temperature. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with ether. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (8/2 hexane/ether) to afford β-keto aldehyde (+)-**9** (0.36 g, 84%) as a clear oil. $[\alpha]^{25}_D$ +78.8 (*c* 0.95, $CHCl_3$). IR (thin film, ν cm^{-1}): 2925, 2949, 1637, 1587, 1409, 1365, 1308, 1250, 1177, 1114, 1076, 1036, 889, 831, 815, 734, 700. ^1H NMR (300 MHz, $CDCl_3$): δ 8.58 (1H, d, J = 3.3 Hz), 7.50 (2H, m), 7.38 (3H, m), 2.46−2.14 (5H, m), 1.91 (1H, m), 1.28 (1H, m), 1.10 (1H, m), 0.32 (6H, d, J = 1.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.1, 185.6, 136.7, 133.9, 129.3, 127.9, 108.8, 32.4, 24.4, 23.7, 20.2, −5.4, −5.4. MS (CI): 261 (MH^+). HRMS (MH^+) calcd for $C_{15}H_{21}O_2Si$ 261.1311, found 261.1318.

Unsaturated β-Keto Aldehyde (+)-10. To a stirring solution of phenylselenenyl chloride (0.55 g, 2.9 mmol) in CH_2Cl_2 (12.0 mL) at 0 °C was added pyridine (0.28 mL, 3.5 mmol). The solution was stirred for 0.75 h, then a solution of β-keto aldehyde (+)-**9** (0.60 g, 2.3 mmol) in CH_2Cl_2 (11.0 mL) was added. The mixture was stirred for 0.25 h at 0 °C and 0.75 h at room temperature. It was then extracted twice with 1 M HCl. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (95/5 hexane/ether) to afford the selenide (0.84 g, 88%) as a yellow oil (mixture of diastereoisomers). $[\alpha]^{25}_D$ +169 (*c* 0.74, $CHCl_3$). IR (thin film, ν cm^{-1}): 3069, 2953, 2851, 1706, 1690, 1438, 1260, 1194, 1114, 1022, 813, 739, 701. ^1H NMR (300 MHz, $CDCl_3$): δ 9.89 and 9.20 (1H, 2 d, J = 0.5 and 1.1 Hz), 7.54−7.26 (10H, m), 2.91 (<1H, t, J = 14.7 Hz), 2.65 (<1H, dt, J = 15.0 and 1.2 Hz), 2.23 (1H, m), 2.15−1.88 (3H, m), 1.79 (1H, m), 1.35 (1H, m), 0.38 and 0.29 (6H, 2 s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.6, 205.4, 194.1, 187.1, 138.3, 137.8, 133.9, 133.8, 130.4, 129.8, 129.5, 129.1, 128.0, 70.0, 61.7, 43.3, 39.4, 34.8, 31.6, 26.5, 26.4, 24.5, 22.0, −5.4, −5.4. MS (EI): 416 (M^+), 388 (M^+ − CO). HRMS (M^+ − CO) calcd for $C_{20}H_{24}OSeSi$ 388.0762, found 388.0771. To a stirring solution of the above selenide (0.24 g, 0.58 mmol) in CH_2Cl_2 (5.8 mL) was added 35% aqueous H_2O_2 (0.10 mL, 1.2 mmol). The mixture was stirred vigorously for 5 min, then another portion of 35% aqueous H_2O_2 (0.10 mL, 1.2 mmol) was added and the mixture was stirred vigorously for another 5 min. The reaction mixture was extracted twice with water. The solvent was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The unsaturated β-keto aldehyde (+)-**10** (0.16 g, quant.) obtained was used directly in the next step without purification because of its high instability.

***β*-Keto Ester 18.** Magnesium (13.3 g, 0.55 mol) was added to methanol (375 mL) and the suspension was stirred at reflux for 1 h then cooled to room temperature. A solution of the cyclopropane **17** (9.2 g, 0.055 mol) in methanol (41.0 mL) was then added and the mixture was stirred for 0.5 h at room temperature and 0.5 h at reflux. After the solution was cooled to 0 °C, 10% HCl was added and the mixture was extracted with ether. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified twice by flash chromatography (9/1 to 1/1 hexane/ether) to give the β-keto ester **18** (8.1 g, 74%) as an oil. IR (thin film, ν cm^{-1}): 2973, 2824, 1758, 1728, 1436, 1376, 1340, 1283, 1200, 1118, 1025. ^1H NMR (300 MHz, $CDCl_3$): δ 3.68 (3H, s), 3.24 (3H, s), 3.20 (1H, m), 3.04 (1H, d, J = 10.7 Hz), 2.66 (1H, m), 2.32 (2H, m), 2.05 (1H, m), 1.59 (1H, m), 1.11 (3H, d, J = 6.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.8, 170.3, 79.6, 58.7, 56.4, 52.3, 47.5, 38.4, 23.9, 16.6. MS (EI): 200 (M^+), 185 (M^+ − CH_3), 168 (M^+ − CH_3OH). HRMS (M^+) calcd for $C_{10}H_{16}O_4$ 200.1048, found 200.1043.

Lactones (+)-19 and (−)-20. To a stirring solution of β-keto ester **18** (8.1 g, 0.040 mol) in toluene (360 mL) was added (*R*)-(−)-pantolactone ((−)-**40**) (6.3 g, 0.049 mol) and DMAP (2.5 g, 0.020 mol). The solution was heated at reflux, with a Dean−Stark apparatus, for 16 h. The reaction mixture was cooled to room temperature and filtered through a silica gel pad. The pad was rinsed with ether and the combined filtrates were concentrated under reduced pressure. The crude product was purified by flash chromatography (7/3 to 3/7 hexane/ether) to afford lactone (+)-**19** (5.13 g, 43%) and lactone (−)-**20** (3.91 g, 32%). Both products were recrystallized in hexane/ether to give white needles. (+)-**19**: mp 51−54 °C. $[\alpha]^{25}_D$ +30.3 (*c* 1.30, $CHCl_3$). IR (thin film, ν cm^{-1}): 3479, 2972, 1798, 1781, 1770, 1738, 1470, 1372, 1280, 1110, 1011, 914, 733. ^1H NMR (300 MHz, $CDCl_3$): δ 5.41 (1H, s), 4.02 (2H, d, J = 4.5 Hz), 3.32 (3H, s), 3.26 (1H, m), 3.22 (1H, d, J = 11.1 Hz), 2.74 (1H, m), 2.40 (2H, m), 2.11 (1H, m), 1.64 (1H, m), 1.18−1.05 (9H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.0, 172.1, 169.1, 79.9, 76.2, 75.5, 58.9, 56.5, 47.7, 40.5, 38.5, 23.8, 22.8, 19.7, 16.7. MS (EI): 298 (M^+). HRMS (M^+) calcd for $C_{15}H_{22}O_6$ 298.1416, found 298.1422. (−)-**20**: mp 91−93 °C. $[\alpha]^{25}_D$ −35.1 (*c* 2.63, $CHCl_3$). IR (thin film, ν cm^{-1}): 2974, 1791, 1761, 1733, 1466, 1378, 1116, 1013. ^1H NMR (300 MHz, $CDCl_3$): δ 5.33 (1H, s), 3.98 (2H, s), 3.26 (3H, s), 3.25 (1H, m), 3.19 (1H, d, J = 10.5 Hz), 2.73 (1H, m), 2.33 (2H, m), 2.08 (1H, m), 1.69 (1H, m), 1.17 and 1.02 (6H, 2 s), 1.16 (3H, d, J = 6.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.9, 171.8, 168.9, 79.1, 76.0, 75.3, 58.2, 56.2, 47.7, 40.5, 38.3, 24.0, 22.9, 19.6, 16.6. MS (EI): 298 (M^+). HRMS (M^+) calcd for $C_{15}H_{22}O_6$ 298.1416, found 298.1422.

***β*-Keto Ester (−)-18.** A solution of lactone (−)-**20** (3.9 g, 0.013 mol) in methanol (100 mL) was placed in a sealed tube under an argon atmosphere and heated in an oil bath at 105 °C for 3 days. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and purified by flash chromatography (8/2 to 6/4 hexane/ether) to afford β-keto ester (−)-**18** (2.5 g, 95%), which was recrystallized in hexane to give a white solid as an analytically pure material. Mp 50−51 °C. $[\alpha]^{25}_D$ −85.2 (*c* 0.89, $CHCl_3$). IR (thin film, ν cm^{-1}): 2974, 2825, 1759, 1728, 1436, 1376, 1340, 1283, 1200, 1118. ^1H NMR (300 MHz, $CDCl_3$): δ 3.72 (3H, s), 3.28 (3H, s), 3.24 (1H, quint, J = 6.4 Hz), 3.08 (1H, d, J = 10.7 Hz), 2.70 (1H, m), 2.32 (2H, m), 2.08 (1H, m), 1.63 (1H, m), 1.14 (3H, d, J = 6.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.8, 170.3, 79.6, 58.8, 56.4, 52.3, 47.5, 38.4, 23.9, 16.6. MS (EI): 200 (M^+), 185 (M^+ − CH_3), 168 (M^+ − CH_3OH). HRMS (M^+) calcd for $C_{10}H_{16}O_4$ 200.1048, found 200.1051.

Methyl Ketone (−)-22. To a stirring solution of β-keto ester (−)-**21** (2.5 g, 0.012 mol) in benzene (70.0 mL) was added K_2CO_3 (2.4 g, 0.017 mol) and methyl vinyl ketone (1.5 mL, 0.017 mol). The solution was stirred for 3 h at room temperature then a second portion of methyl vinyl ketone (1.5 mL, 0.017 mol) was added. The solution was stirred another 16 h at room temperature. A third portion of methyl vinyl ketone (1.5 mL, 0.017 mol) was added and the solution was stirred for 24 h at room temperature. Water was added to quench the reaction mixture and it was extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude methyl ketone (−)-**22** (3.1 g, 92%) as a light yellow oil. $[\alpha]^{25}_D$ −91.4 (*c* 1.74, $CHCl_3$). IR (thin film, ν cm^{-1}): 2972, 1751, 1731, 1715, 1435, 1374, 1230, 1196, 1167, 1110. ^1H NMR (300 MHz, $CDCl_3$): δ 3.69 (3H, s), 3.20 (3H, s), 3.17 (1H, m), 2.70 (1H, m), 2.57−2.12 (6H, m), 2.12 (3H, s), 1.99 (1H, m), 1.69 (1H, m), 1.16 (3H, d, J = 6.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.6, 208.3, 170.7, 78.6, 61.6, 56.0, 52.3, 51.8, 38.9, 38.5, 29.7, 28.2, 23.8, 16.9. MS (EI): 270 (M^+). HRMS (M^+) calcd for $C_{14}H_{22}O_5$ 270.1467, found 270.1460.

Enone (+)-23. To a stirring solution of methyl ketone (−)-**22** (3.1 g, 0.011 mol) in benzene (113 mL) was added pyrrolidine (2.4 mL, 0.028 mol). The solution was heated at reflux, under a Dean−Stark apparatus, for 16 h. Pyrrolidine (2.4 mL, 0.028 mol) was added and the mixture was again heated at

reflux for 8 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was dissolved in benzene (46.0 mL) and a solution of NaOAc (0.46 g, 5.6 mmol) and acetic acid (0.91 mL) in water (22.6 mL) was added. The reaction mixture was stirred at reflux for 4 h and cooled to room temperature, then it was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (6/4 to 1/1 hexane/ether) to afford enone (+)-**23** (2.0 g, 70%), which was recrystallized in hexane to give a yellow solid as an analytically pure material. Mp 50−52 °C. $[\alpha]^{25}_D$ +111 (*c* 0.99, $CHCl_3$). IR (thin film, ν cm^{-1}): 2950, 1730, 1670, 1447, 1330, 1232, 1198, 1168, 1097. ^1H NMR (300 MHz, $CDCl_3$): δ 5.84 (1H, s), 3.73 (3H, s), 3.28 (3H, s), 3.11 (1H, m), 3.05 (1H, m), 2.90 (1H, qt, J = 11.1 and 2.1 Hz), 2.63−2.32 (3H, m), 1.98−1.61 (4H, m), 1.13 (3H, d, J = 6.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.3, 171.7, 171.1, 123.7, 78.8, 57.2, 56.7, 56.0, 52.0, 34.9, 34.1, 30.7, 25.8, 17.6. MS (EI): 252 (M^+). HRMS (M^+) calcd for $C_{14}H_{20}O_4$ 252.1361, found 252.1365.

Allyl Ester (+)-33. To a stirring solution of Nazarov intermediate (−)-**29** (0.23 g, 0.53 mmol) in CH_2Cl_2 (10.0 mL) was added Cs_2CO_3 (0.34 g, 1.0 mmol) and the mixture was stirred at room temperature for 10 min then cooled to 0 °C. A solution of unsaturated β-keto aldehyde (+)-**10** (0.27 g, 1.0 mmol) in CH_2Cl_2 (9.4 mL) was added to the reaction mixture and stirring continued at 0 °C for 0.75 h. The solution was then diluted with EtOAc and filtered through a pad of Celite. The pad was rinsed with EtOAc and the solvent was concentrated under reduced pressure. The crude product was purified by flash chromatography (8/2 to 1/1 hexane/ether) to afford allyl ester (+)-**33** (0.35 g, 97%) as a yellow oil (mixture of keto−enol). $[\alpha]^{25}_D$ +8.2 (*c* 2.03, $CHCl_3$). IR (thin film, ν cm^{-1}): 2953, 1752, 1735, 1693, 1660, 1428, 1399, 1374, 1237, 1217, 1113, 1047, 912, 816, 734, 703. ^1H NMR (300 MHz, $CDCl_3$): δ 12.16 (<1H, s), 9.18 (1H, d, J = 1.0 Hz), 7.45 (2H, m), 7.35 (3H, m), 5.86 (1H, m), 5.34−5.24 (3H, m), 4.61 (2H, qd, J = 13.0 and 5.8 Hz), 3.66 (3H, s), 3.32 (1H, dd, J = 9.0 and 4.1 Hz), 3.20 (3H, s), 3.06 (2H, m), 2.79 (1H, m), 2.64 (2H, d, J = 15.2 Hz), 2.47 (2H, dd, J = 12.6 and 6.5 Hz), 2.38 (1H, d, J = 8.9 Hz), 2.22 (5H, m), 2.00 (2H, m), 1.75 (3H, s), 1.71 (1H, m), 1.50 (1H, m), 1.15 (3H, d, J = 5.9 Hz), 0.31 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.8, 199.0, 171.8, 170.8, 170.7, 170.4, 162.0, 136.8, 133.9, 131.7, 129.4, 128.0, 127.9, 127.8, 119.2, 98.9, 79.1, 69.1, 65.4, 62.0, 55.6, 52.2, 48.3, 40.2, 38.9, 37.6, 36.7, 36.2, 29.9, 29.0, 23.1, 20.7, 16.8, −3.8, −4.2. MS (EI): 696 (M^+). HRMS (M^+) calcd for $C_{37}H_{48}O_{11}Si$ 696.2966, found 696.2955.

Tricycle (+)-34. To a stirring solution of allyl ester (+)-**33** (0.35 g, 0.51 mmol) in THF (10.0 mL) was added $Pd(PPh_3)_4$ (0.019 g, 0.017 mmol) and morpholine (0.22 mL, 2.5 mmol). The reaction mixture was stirred at room temperature for 0.5 h and the solvent was then removed in vacuo. The crude product was purified by flash chromatography (1/1 to 0/1 hexane/ether) to afford tricycle (+)-**34** (0.19 g, 62%) as a white solid. $[\alpha]^{25}_D$ +80.1 (*c* 1.07, $CHCl_3$). IR (thin film, ν cm^{-1}): 2953, 1753, 1732, 1428, 1375, 1231, 1111, 1042, 912, 836, 734. ^1H NMR (300 MHz, $CDCl_3$): δ 9.48 (1H, s), 7.41 (2H, m), 7.34 (3H, m), 5.00 (1H, t, J = 8.4 Hz), 3.66 (3H, s), 3.23 (1H, m), 3.18 (3H, s), 3.08 (1H, m), 2.97 (1H, m), 2.79 (1H, m), 2.62−2.12 (11H, m), 1.99 (1H, m), 1.83 (3H, s), 1.75 (1H, m), 1.52 (2H, m), 1.19 (3H, d, J = 6.0 Hz), 0.29 (6H, d, J = 2.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.2, 208.6, 207.4, 198.6, 170.6, 170.4, 135.9, 133.7, 129.6, 128.0, 79.3, 68.8, 67.4, 61.8, 55.9, 52.2, 48.6, 42.8, 40.5, 39.5, 37.9, 37.8, 36.7, 28.1, 23.4, 21.5, 21.0, 16.8, −5.2. MS (EI): 584 (M^+ − CO), 581 (M^+ − OMe), 552 (M^+ − CH_3CO_2H). HRMS (M^+ − CO) calcd for $C_{32}H_{44}O_8Si$ 584.2805, found 584.2800. HRMS (M − OMe)$^+$ calcd for $C_{32}H_{41}O_8Si$ 581.2570, found 581.2578.

Alcohol (−)-35. To a stirring solution of tricycle (+)-**34** (0.020 g, 0.033 mmol) in THF (0.70 mL) at −78 °C was added lithium tris[(3-ethyl-3-pentyl)oxy]aluminohydride (0.5 M in THF) (0.072 mL, 0.036 mmol) dropwise. The reaction mixture was then stirred at −45 °C for 16 h. Lithium tris[(3-ethyl-3-pentyl)oxy]aluminohydride (0.5 M in THF) (0.036 mL, 0.018 mmol) was added and the mixture was stirred another 6 h at −45 °C. The mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (4/6 to 0/1 hexane/ether) to afford alcohol (−)-**35** (0.014 g, 72%) as a white solid. $[\alpha]^{25}_D$ −0.69 (*c* 1.45, $CHCl_3$). IR (thin film, ν cm^{-1}): 3458, 3015, 2954, 1754, 1732, 1714, 1428, 1375, 1236, 1198, 1112, 1050, 953, 816, 754, 703, 668. ^1H NMR (300 MHz, $CDCl_3$): δ 7.44 (2H, m), 7.35 (3H, m), 5.14 (1H, d, J = 9.7 Hz), 4.24 (1H, d, J = 12.5 Hz), 4.05 (1H, t, J = 9.8 Hz), 3.66 (3H, s), 3.31 (1H, m), 3.14 (3H, s), 3.12 (1H, m), 3.01 (1H, q, J = 4.2 Hz), 2.73 (1H, m), 2.57 (3H, m), 2.50−1.93 (9H, m), 1.91 (3H, s), 1.70 (3H, m), 1.49 (1H, dt, J = 14.3 and 5.4 Hz), 1.14 (3H, d, J = 5.9 Hz), 0.32 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.8, 213.3, 209.8, 171.7, 170.4, 136.2, 133.8, 129.5, 128.0, 78.9, 71.2, 62.9, 61.4, 55.9, 55.8, 52.2, 49.1, 43.0, 40.6, 39.6, 38.9, 37.8, 37.6, 35.8, 27.1, 23.8, 22.6, 21.2, 16.9, −4.7, −4.8. MS (EI): 614 (M^+). HRMS (M^+) calcd for $C_{33}H_{46}O_9Si$ 614.2911, found 614.2917.

Acetate (−)-36. To a solution of alcohol (−)-**35** (0.012 g, 0.020 mmol) in pyridine (1.0 mL) was added acetic anhydride (9.2 μL, 0.098 mmol) and DMAP (0.5 mg, 4.1 μmol). The solution was stirred for 16 h at room temperature, quenched with a saturated aqueous solution of NH_4Cl, and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (95/5 hexane/ether) to give acetate (−)-**36** (0.012 g, 94%) as a light yellow solid. $[\alpha]^{25}_D$ −2.8 (*c* 1.20, $CHCl_3$). IR (thin film, ν cm^{-1}): 2952, 1752, 1736, 1710, 1428, 1375, 1236, 1111, 1031, 912, 817, 732. ^1H NMR (300 MHz, $CDCl_3$): δ 7.44 (2H, m), 7.37 (3H, m), 5.10 (1H, quint, J = 4.3 Hz), 4.61 (1H, s), 3.65 (3H, s), 3.17 (3H, s), 3.06 (1H, m), 3.05 (1H, m), 2.76 (1H, m), 2.54 (4H, m), 2.44 (2H, m), 2.29 (2H, m), 2.23 (2H, m), 2.05 (3H, s), 1.97 (3H, m), 1.87 (3H, s), 1.70 (3H, m), 1.53 (1H, dt, J = 14.1 and 5.8 Hz), 1.18 (3H, d, J = 5.9 Hz), 0.33 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.1, 210.9, 209.3, 170.8, 170.4, 170.1, 136.2, 133.7, 129.6, 128.1, 79.2, 69.8, 63.5, 61.5, 55.8, 53.4, 52.2, 48.2, 43.0, 40.8, 40.3, 38.8, 37.9, 37.8, 34.7, 27.5, 23.4, 22.1, 21.1, 20.7, 16.8, −4.7, −4.8. MS (EI): 656 (M^+). HRMS (M^+) calcd for $C_{35}H_{48}O_{10}Si$ 656.3017, found 656.3021.

Tetracycle (−)-37. To a stirring solution of acetate (−)-**36** (0.052 g, 0.079 mmol) in THF (8.0 mL) was added KHMDS (0.5 M in toluene) (0.079 mL, 0.040 mmol). The reaction mixture was stirred at reflux for 10 min, allowed to cool to room temperature, and filtered through a pad of silica gel. The pad was rinsed with EtOAc and the solvent was removed in vacuo. The crude product was purified by flash chromatography (6/4 to 0/1 hexane/ether) to give tetracycle (−)-**37** (0.018 g, 35%). $[\alpha]^{25}_D$ −0.17 (*c* 1.80, $CDCl_3$). IR (thin film, ν cm^{-1}): 3422, 2953, 1749, 1708, 1428, 1376, 1230, 1156, 1113, 1044, 817, 754. ^1H NMR (300 MHz, $CDCl_3$): δ 7.44 (2H, m), 7.37 (3H, m), 5.32 (1H, s), 4.72 (1H, six, J = 4.3 Hz), 4.60 (1H, d, J = 11.6 Hz), 4.46 (1H, d, J = 11.6 Hz), 3.80 (3H, s), 3.44 (1H, m), 3.09 (3H, s), 2.96 (2H, d, J = 5.2 Hz), 2.60 (3H, m), 2.40 (2H, m), 2.08 (3H, s), 2.06−1.85 (2H, m), 1.84 (3H, s), 1.72 (3H, m), 1.57 (1H, m), 1.26 (4H, m), 1.04 (3H, d, J = 5.9 Hz), 0.30 (6H, d, J = 2.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.4, 205.4, 176.6, 170.4, 168.9, 136.9, 133.6, 129.4, 128.0, 81.9, 78.9, 67.8, 60.9, 56.2, 55.9, 55.7, 54.0, 53.1, 52.1, 44.9, 44.8, 39.9, 39.4, 37.9, 31.5, 28.2, 25.0, 24.3, 20.9, 20.4, 17.1, −3.1, −3.5. MS (EI): 656 (M^+), 641 (M^+ − CH_3), 648 (M^+ − H_2O), 624 (M^+ − CH_3OH). HRMS (M^+) calcd for $C_{35}H_{48}O_{10}Si$ 656.3017, found 656.3007.

Cyclopropane (+)-38. To a stirring solution of acetate (−)-**36** (5.3 mg, 8.1 μmol) in acetonitrile (1.0 mL) was added Cs_2CO_3 (1.5 mg, 4.5 μmol). The solution was heated at reflux for 16 h then cooled to room temperature. The solvent was

removed in vacuo. The crude product was purified by flash chromatography (4/6 to 2/8 hexane/ether) to give cyclopropane (+)-**38** (1.8 mg, 38%). $[\alpha]^{25}_{D}$ +72.7 (*c* 0.11, $CHCl_3$). IR (thin film, ν cm^{-1}): 3384, 2950, 1743, 1711, 1657, 1428, 1379, 1231, 1114, 1041, 816, 754. ^1H NMR (300 MHz, $CDCl_3$): δ 7.41 (5H, m), 6.25 (1H, s), 4.68 (1H, d, J = 11.2 Hz), 4.15 (1H, d, J = 11.3 Hz), 3.73 (3H, s), 3.36 (1H, m), 3.21 (1H, m), 3.12 (3H, s), 2.67 (1H, m), 2.48 (1H, t, J = 14.2 Hz), 2.31−1.89 (7H, m), 2.04 (3H, s), 1.77 (1H, quint, J = 9.5 Hz), 1.58 (2H, m), 1.25 (4H, m), 1.05 (3H, d, J = 5.9 Hz), 0.32 (6H, d, J = 3.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.3, 209.3, 172.4, 170.3, 135.5, 133.7, 129.7, 128.1, 96.7, 79.7, 69.2, 67.6, 59.5, 56.0, 51.4, 51.3, 39.3, 38.3, 37.2, 34.9, 34.9, 31.9, 31.8, 29.6, 26.0, 21.5, 20.6, 18.3, −5.3, −5.6. MS (EI): 596 (M^+), 578 $(M - H_2O)^+$. HRMS (M^+) calcd for $C_{33}H_{44}O_8Si$ 596.2805, found 596.2797.

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Supporting Information Available: Experimental procedures and characterization data for compounds (+)-**11**, (+)-**12**, **15**, **16**, (+)-**24**, (−)-**25**, (−)-**26**, (−)-**27**, (−)-**28**, (−)-**29**, **30**, and **31**, ^1H NMR spectra for all compounds, and X-ray crystal structure for compounds (−)-**20** and (+)-**38**. This material is available free of charge via the Internet at http://pubs.acs.org. The following crystal structures have been deposited at the Cambridge Crystallographic Data Centre: (−)-**20** (CCDC 212046) and (+)-**38** (CCDC 212047).

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