INVESTIGATIONS DIRECTED AT THE TOTAL SYNTHESIS OF OUABAIN. LESSONS LEARNED FROM DEGRADATION STUDIES†

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Abstract – A procedure has been developed for transforming pentacyclic Heck product (**8**) to enone (**10**), an intermediate having appropriate functionality for future elaboration of the C1 and C3 diol functionality of ouabagenin. The plant-derived cardiac glycoside ouabain has been degraded to analogs (**17**) and (**20**) that contain, respectively, a $\Delta^{9,11}$ double bond and C17 nitrile. These intermediates should be useful in future efforts to develop chemistry for functionalizing the $\Delta^{9,11}$ double bond of **8** to incorporate C11 oxidation and for elaborating the β C17 nitrile of this advanced synthetic intermediate to a β butenolide.

† *Dedicated with admiration and friendship to Professor Teruaki Mukaiyama in recognition of his seminal contributions to organic synthesis.*

INTRODUCTION

The cardiac glycosides are a large group of steroids possessing a sugar residue at the 3β position.[1] Named for their dramatic effect on the heart, cardiac glycosides have been used by indigenous populations in Africa and Asia as dart poisons and have also found extensive use in modern medicine in the treatment of congestive heart failure.[2] Cardiac glycosides have been isolated from both plant and animal sources.[3] Extracts of *strophanthus* and *digitalis* plants provide the cardiac glycosides ouabain (**1**) and digitoxin (**3**) (Figure 1). The aglycones of ouabain (ouabagenin, **2**) and digitoxin (digitoxigenin, **4**) represent a class of steroids known as cardenolides that differ from other steroids in having a β-oriented butenolide ring at

C17, a *cis* C/D ring fusion and an angular hydroxyl substituent at C14. In addition, most cardenolides also have a *cis* A/B ring fusion.

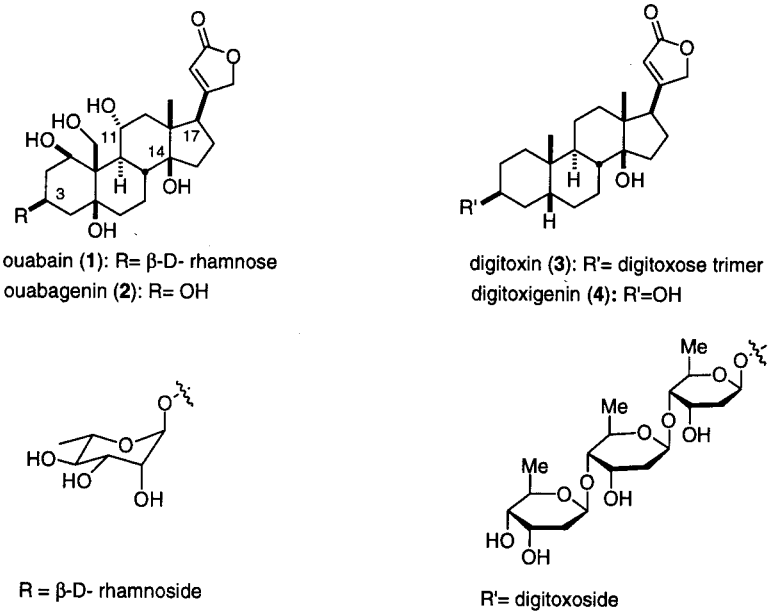


Figure 1. Representitive cardiac glycosides: (–)-ouabain (**1**) and (+)-digitoxin (**3**).

Cardiac glycosides and other cardiac steroids elicit their effect by binding to myocardial Na^+,K^+-ATPase, an enzyme responsible for regulating intracellular Na^+ transport.[4] The existence of a steroid-binding site in cardiovascular Na^+,K^+-ATPase implies that an endogenous regulatory factor could exist.[5] A recent communication by Nakanishi and coworkers[6] reports persuasive evidence for the presence of physiological ouabain in bovine hypothalamus. This finding, in conjunction with sodium pump assays,[7] provides strong justification for believing that ouabain, or a complex of ouabain with an inorganic acid, is an endogenous factor in mammals.

The high level of oxidation of the steroid skeleton and the *cis* A/B and C/D ring fusions make complex cardenolides challenging targets for total synthesis. The recent total synthesis of digitoxigenin by Stork and co-workers[8] is the singular total synthesis of a cardenolide natural product. All other endeavors have been partial syntheses from steroid starting materials.[9,10] *Strophanthus* cardenolides such as ouabain pose a more formidable synthetic challenge than digitoxigenin owing to their extensive additional oxidation.[11] Herein we report our most recent progress towards the total synthesis of ouabagenin and disclose results of degradation studies of ouabain that were conducted as adjuncts to our total synthesis endeavors.

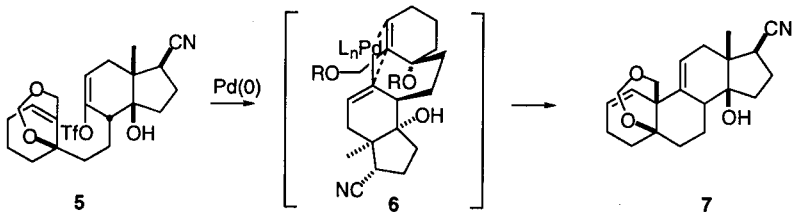
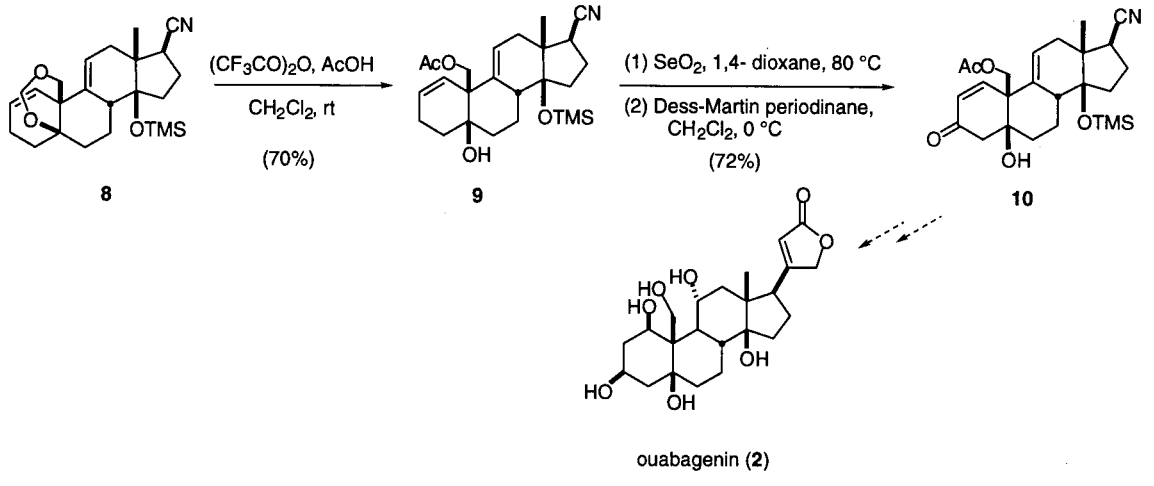


Figure 2. Intramolecular Heck approach to the synthesis of cardenolides.

RESULTS AND DISCUSSION

Synthetic Strategy and Introduction of Oxidation at C3. Our total synthesis approach to ouabagenin features an intramolecular Heck reaction to fashion the B ring and establish the *cis* A/B ring fusion (Figure 2).[12] One demonstration of this strategy generated steroid (**7**) that embodies many structural features of complex *strophanthus* cardenolides, although it lacks oxidation at C1, C3 and C11.[13] Since our initial report of the synthesis of **7**, we have made some progress in further functionalizing the A-ring of this intermediate. Early scouting studies indicated that **7** was a poor template for introducing oxidation at C3 due to the low reactivity of the $\Delta^{1,2}$ double bond and the sensitivity of the methylene acetal. However, the situation was much improved if the methylene acetal was first opened (Scheme 1). Conversion of **7** to trimethylsilyl (TMS) derivative (**8**),[13] followed by cleavage of the methylene acetal of **8** by reaction with trifluoroacetic anhydride and acetic acid provided tetracyclic acetate (**9**). Allylic oxidation of this intermediate with SeO_2, and further oxidation of the resulting C3 allylic alcohol with Dess-Martin periodinane provided enone (**10**) in 50% overall yield from **8**.

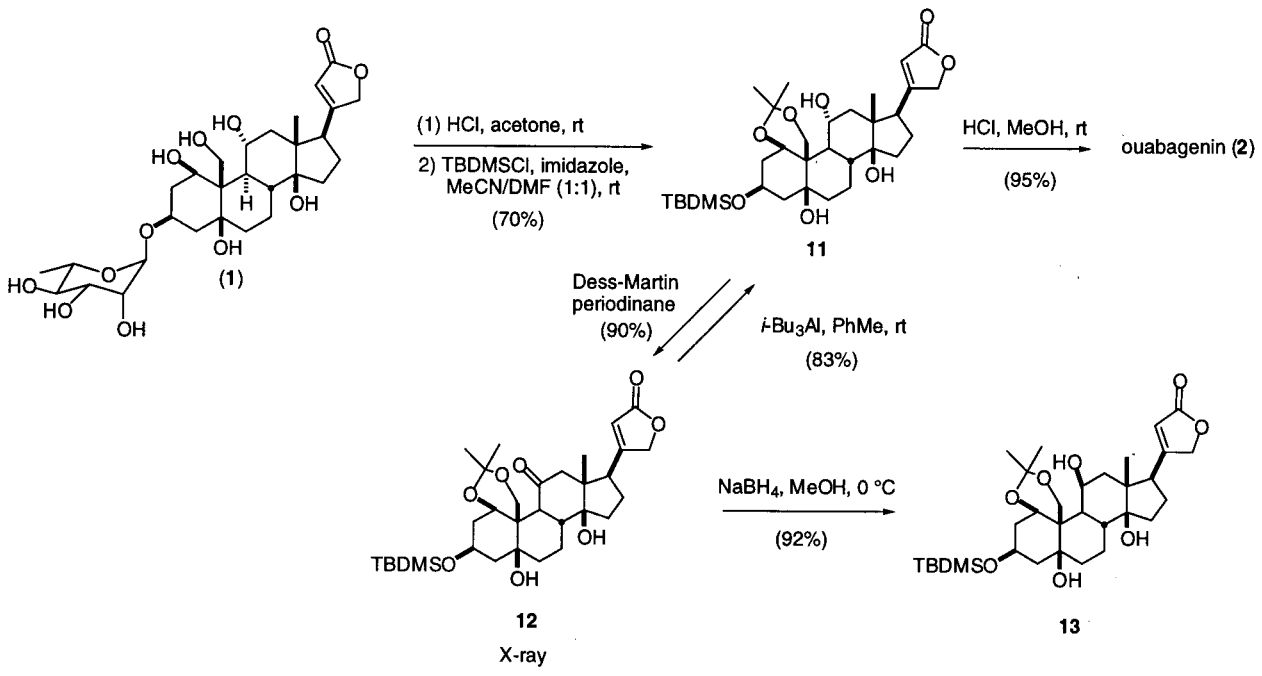
Scheme 1



Having introduced essential oxidation at C3, several significant problems remain to be solved before an intermediate such as **10** can be converted to ouabagenin: converting the ring A enone to a *cis* 1,3-diol, functionalizing the $\Delta^{9,11}$ double bond to incorporate oxidation at C11, and elaboration of the C17 nitrile to a β-oriented butenolide. To simplify the development of chemistry for accomplishing the latter two of these objectives, we turned to degradation of ouabain. The initial goal was to degrade ouabain to analogs that contain the C17 nitrile and the $\Delta^{9,11}$ double bond functionalities.

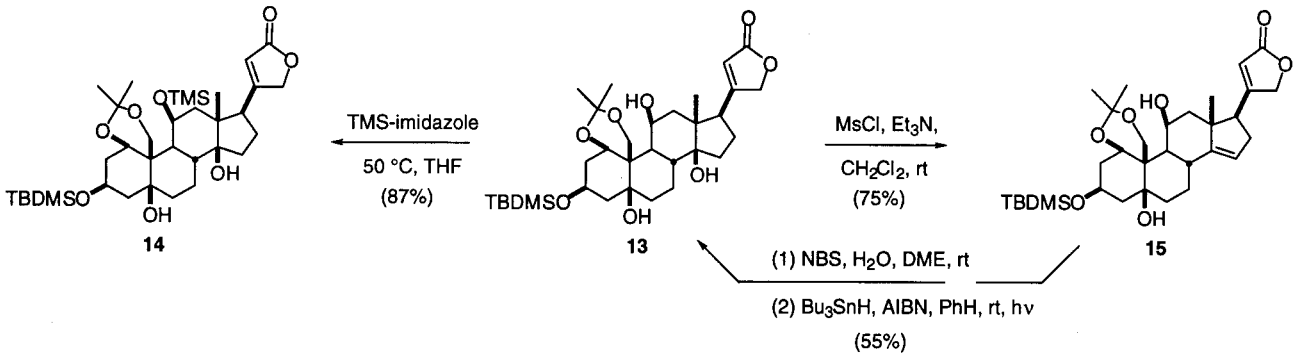
Degradation of Ouabain. Fortunately, there was considerable guidance on how to proceed from the extensive degradation studies carried out during early structural investigations of ouabain and related *strophanthus* cardenolides.[1] We began by converting ouabain (**1**) to a ouabagenin mono-acetonide by the method of Mannich;[14] subsequent selective protection of the C3 hydroxyl group of this intermediate with *tert*-butyldimethylsilyl chloride furnished silyl ether (**11**) (Scheme 2). Ouabagenin (**2**) could be readily regenerated by exposure of **11** to HCl and MeOH. Smooth oxidation of the C11 alcohol of **11** was realized with Dess-Martin periodinane[15] to yield ketone (**12**), the structure of which was confirmed by single crystal X-ray analysis.[16] Reduction of **12** with $NaBH_4$ furnished axial alcohol (**13**) stereoselectively, as would be expected from existing precedent.[17] Alternatively, the desired C11 equatorial hydroxyl group of ouabagenin derivative (**11**) could be restored in high yield, without detrimental effects to the butenolide, by reduction of **12** with triisobutylaluminum.[18]

Scheme 2



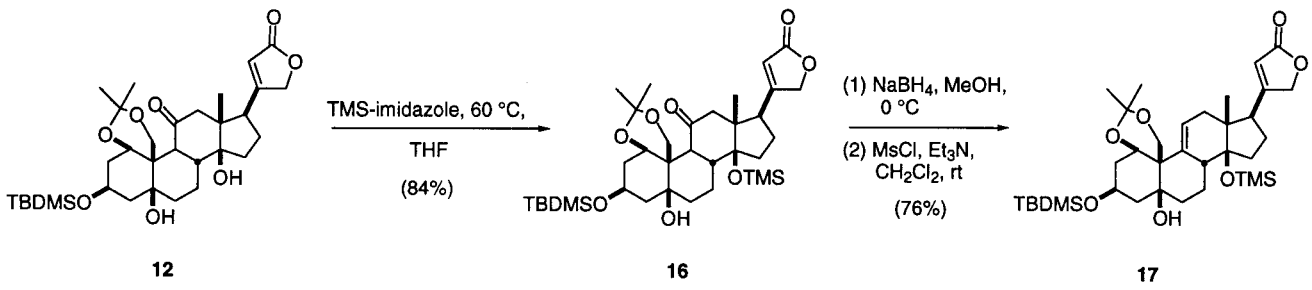
With axial alcohol (**13**) in hand, we turned to installing the $\Delta^{9,11}$ double bond into the ouabagenin skeleton (Scheme 3). There are several reports that cortical steroids having the β configuration at C11 can be smoothly eliminated to steroids containing $\Delta^{9,11}$ unsaturation.[19] However, exposure of **13** to methanesulfonyl chloride (MsCl) and Et_3N at room temperature cleanly introduced a $\Delta^{14,15}$ double bond to generate **15**. The structure of **15** followed from ^{13}C NMR studies (DEPT 90 and 135) that clearly show the presence of a trisubstituted double bond and three R_2CHOR' carbons corresponding to carbons 1, 3 and 11.[20] That the relative reactivities of the secondary C11 and tertiary C14 hydroxyl groups are similar was apparent in reactions of **13** with common silylating reagents which provided mixtures of mono-silyl products. However, silylation of **13** with 1-(trimethylsilyl)imidazole resulted in selective protection of the C11 alcohol to generate **14**.[21]

Scheme 3



It was possible to regenerate the βC14 alcohol from **15** without compromising the butenolide unit (Scheme 3). Thus, reaction of **15** with *N*-bromosuccinimide (NBS) and H_2O in 1,2-dimethoxyethane (DME) selectively yielded the C14,15 bromohydrin. Tin hydride debromination of this intermediate provided **13** in 55% overall yield.

Scheme 4

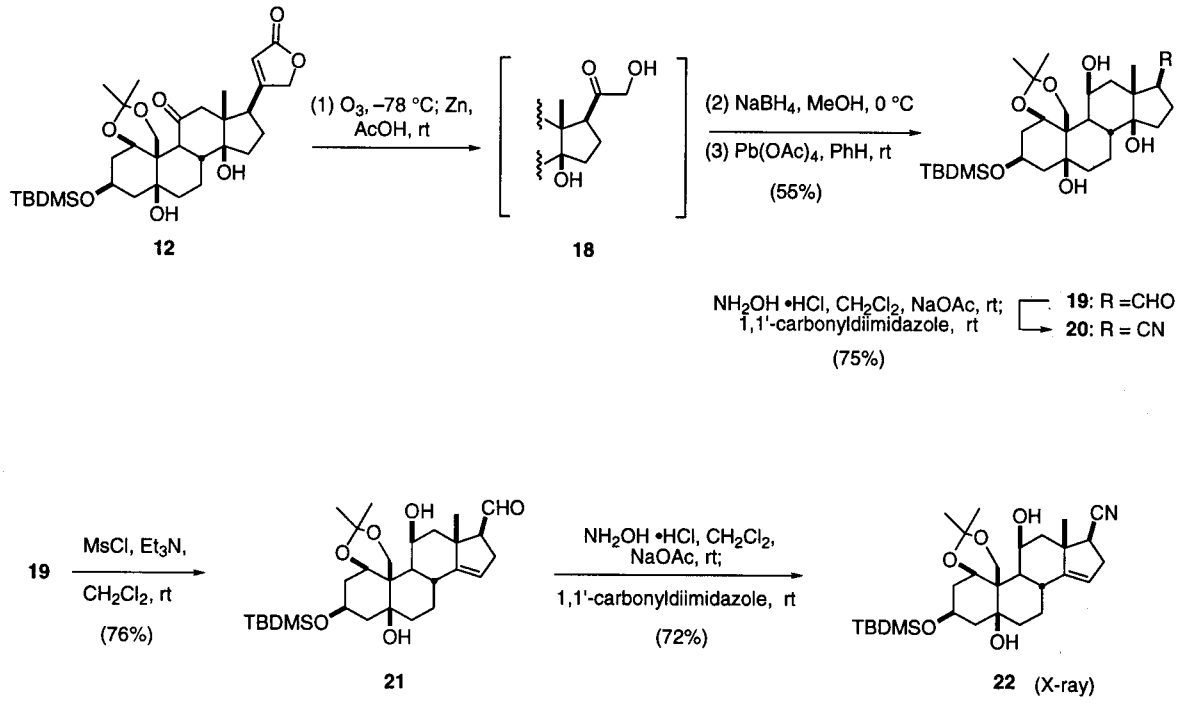


Installation of the 9,11 double bond into the ouabagenin skeleton could be accomplished by first masking the C14 alcohol (Scheme 4). Reaction of **12** with *N*-trimethylsilylimidazole selectively generated **16**.

Borohydride reduction of **16** gave the β C11 alcohol, and dehydration of this intermediate with MsCl and Et_3N delivered **17** in 64% overall yield from **12**. That the double bond had finally been installed in the $\Delta^{9,11}$ position was confirmed by ^{13}C NMR experiments (DEPT 90 and 135) which showed that **17** had a trisubstituted double bond and two R_2CHOR' carbons (C1 and C3).

Owing to the sensitivity of the butenolide, the projected endplay of our current approach to ouabagenin envisages transformation of a β C17 nitrile to a β butenolide. Although just such an elaboration was an important element of the Stork synthesis of digitoxigenin,[8] in the ouabagenin series this transformation would have to be accomplished on much more densely functionalized intermediates. Thus, we turned to degradation of **12** to provide a C17 nitrile intermediate appropriate for evaluating this chemistry (Scheme 5). Oxidation of **12** with ozone and subsequent reduction with Zn and acetic acid generated the unstable α-hydroxy ketone (**18**). Without isolation, **18** was reduced to the 1,2-diol and this latter intermediate was cleaved with lead tetraacetate to give aldehyde (**19**) in 50% overall yield from **12**. Standard conversion of this intermediate to the oxime and dehydration with 1,1'-carbonyldiimidazole provided nitrile (**20**) in 75% yield. Exposure of aldehyde (**19**) to methanesulfonyl chloride and Et_3N generated the $\Delta^{14,15}$ alkene derivative (**21**), which was converted in a similar fashion to β C17 nitrile (**22**). The structure of **22** was unambiguously established using single crystal X-Ray analysis (Scheme 5).[16]

Scheme 5



CONCLUSION

Chemistry has been developed for elaborating pentacyclic Heck product (**8**) to enone (**10**), an intermediate that would appear to have requisite functionality for future evolution of the *cis* C1, C3 diol functionality of ouabagenin. To facilitate developing chemistry for functionalizing the $\Delta^{9,11}$ double bond and C17 nitrile of **8**, ouabain has been degraded to derivatives that contain these functionalities.

ACKNOWLEDGMENTS

This research was supported by NIH grant GM-30859 and fellowships to P.V.R. from the Department of Education (P200A10156-93 and P200A40137-95). We are grateful to Dr. Joseph Ziller for X-Ray analyses of **12** and **22**, and Drs. John Greaves and John Mudd for mass spectrometric analyses. NMR and mass spectra were determined at UCI using instrumentation acquired with the assistance of NSF and NIH Shared Instrumentation programs.

EXPERIMENTAL SECTION

General experimental details. The solvents THF, Et_2O, CH_2Cl_2, and toluene were dried by passage through a bed of activated alumina: A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, and F. J. Timmers, *Organometallics,* 1996, **15**, 1518. For reactions requiring anhydrous conditions, substrates were dried by azeotropic distillation using benzene or toluene. Exact mass measurements were obtained by the liquid secondary ion mass spectrometry method (LSIMS) on a *Micromass Autospec* instrument or by electrospray time of flight (ES TOF) on a *Micromass LCT* instrument. Chromatography was performed using E. Merck silica gel (SiO_2, 60 Å). Other experimental details were described recently: K. P. Minor and L. E. Overman, *J. Org. Chem.,* 1997, **62**, 6379. Room temperature (*ca.* 23 °C) is abbreviated as rt; other standard abbreviations used are listed in *J. Org. Chem., 1999*, **64**, 21A.

10-Acetyloxymethyl-17-cyano-5,14-dihydroxy-13-methyl-3,4,5,6,7,8,12,13,14,15,16,17-dodecahydrocyclopenta[*a*]phenanthrene (9). Freshly distilled trifluoroacetic anhydride (0.40 mL, 2.9 mmol) was added dropwise to a solution of steroid (**8**)[13] (20 mg, 0.048 mmol), CH_2Cl_2 (6 mL) and glacial AcOH (0.10 mL, 2.3 mmol) at 0 °C. The reaction was allowed to stand for 30 min and another portion of

trifluoroacetic anhydride (0.40 mL, 2.9 mmol) was added dropwise. The solution was warmed to rt and maintained until complete consumption of starting material (approximately 0.5 h). The reaction was poured into a saturated aqueous solution of $NaHCO_3$ (100 mL) and extracted with EtOAc (3 × 100 mL). The organic layers were combined, concentrated and dried (Na_2SO_4) to afford a dark yellow oil. Flash chromatography (4:1 to 1:1 hexane-EtOAc) gave **9** (15 mg, 70%) as a clear oil along with its C14 desilylated congener (1 mg, 6%). Data for **9**: $[\alpha]_D^{24}$ = +80.0°, $[\alpha]_{546}^{24}$ = +252° (*c* 0.10, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.90 (br d, *J* = 10.0 Hz, 1H), 5.68 (d, *J* = 10.0 Hz, 1H), 5.34–5.32 (m, 1H), 4.51 (d, *J* = 11.4 Hz, 1H), 4.21 (d, *J* = 11.4 Hz, 1H), 2.62 (dd, *J* = 9.5, 4.5 Hz, 1H), 2.33–2.04 (m, 6H), 2.06 (s, 3H), 1.95–1.63 (m, 7H), 1.38–1.28 (m, 3H), 1.18 (s, 3H), 0.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.4, 140.3, 128.8, 127.6, 123.2, 122.2, 88.4, 72.3, 66.1, 49.9, 28.2, 40.4, 38.9, 38.7, 35.1, 34.1, 30.5, 25.8, 25.4, 22.4, 21.5, 12.0, 2.8; IR (film) 3497, 2931, 2244, 1732, 1603, 1465, 1371, 1238, 1101 cm^{-1}; HRMS (ES TOF) *m/z* 466.2411 (466.2390 calcd for $C_{25}H_{37}NO_4NaSi$, M+Na).

10-Acetyloxymethyl-17-cyano-5,14-dihydroxy-13-methyl-3-oxo-3,4,5,6,7,8,12,13,14,15,16,17-dodecahydrocyclopenta[*a*]phenanthrene (10). A mixture of acetate (**9**) (15 mg, 0.034 mmol), 1,4-dioxane (2.0 mL) and SeO_2 (150 mg, 1.4 mmol) was heated to 80 °C for 24 h (until complete consumption of starting material). The reaction was allowed to cool to rt and was diluted with EtOAc (100 mL) and washed with $NaHCO_3$ (100 mL). The aqueous layer was further extracted with EtOAc (3 × 20 mL) and the organic layers were combined, dried (Na_2SO_4) and concentrated. The resulting intermediate C3 allylic alcohol was dissolved in CH_2Cl_2 (1.0 mL) and cooled to 0 °C. Dess-Martin periodinane (20 mg, 0.047)[15] was added, the resulting solution was maintained at 0 °C for 15 min, and saturated aqueous $NaHCO_3$ (50 mL) was added. This mixture was extracted with EtOAc (3 × 50 mL) and the organic extracts were combined, dried ($NaSO_4$), and concentrated. The resulting residue was purified by flash chromatography (1:3 EtOAc-hexanes) to furnish 11 mg of enone(**10**)(71%) as a thick oil: $[\alpha]_D^{24}$ = +127° (*c* 0.13, $CDCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.90 (d, *J* = 13.0 Hz, 1H), 6.22 (d, *J* = 13.0 Hz, 1H), 5.40 (app d, *J* = 7.0 Hz, 1H), 4.62 (d, *J* = 13.5 Hz, 1H), 4.65 (d, *J* = 13.5 Hz, 1H), 2.90–2.82 (m, 1H) 2.61 (dd, *J* = 11.5, 4.5 Hz, 1H), 2.32–1.60 (m, 10H), 2.06 (s, 3H), 1.34–1.20 (m, 3H), 1.27 (s, 3H), 0.25 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.9, 173.9, 152.4, 149.9, 129.3, 124.4, 122.8, 88.1, 76.6, 64.6, 51.4, 48.1, 40.1, 38.8, 35.5, 34.3, 30.1, 26.2, 25.7, 23.1, 21.4, 17.1, 2.9; IR (film) 3443, 2933, 2234,

1740.1, 1681, 1608, 1250, 1226, 1103, 1057 cm^{-1}; HRMS (ES TOF) *m/z* 480.2170 (480.2182 calcd for $C_{25}H_{35}NO_5NaSi$, M+Na).

1,19-Acetonide-3-(*tert*-butyldimethylsiloxy)ouabagenin (11). A solution of ouabagenin 1,19-monoacetonide (10.0 g, 20.9 mmol),[14] *tert*-butyldimethylsilyl chloride (TBDMSCl, 4.10 g, 27.0 mmol) and DMF/MeCN (1:1, 100 mL) was maintained for 12 h at rt. Methanol (20 mL) was added and the mixture was poured into EtOAc (1.0 L) and washed with saturated brine (200 mL). The aqueous layer was further extracted with EtOAc (3 × 200 mL) and the organic extracts were combined, dried (Na_2SO_4) and concentrated to afford a colorless powder that was dried under vacuum (1 mm Hg, rt) for 48 h to furnish 12.0 g (97%) of **11**, which was used without further purification. An analytical sample was obtained by recrystallization from MeOH-EtOAc (1:10) to furnish **11** as a colorless powder: mp 185 °C; $[\alpha]_D^{24}$ = + 59.1° $[\alpha]_{577}^{24}$ + 64.5°, $[\alpha]_{546}^{24}$ = + 75.4°, $[\alpha]_{435}^{24}$ = + 123°, $[\alpha]_{405}^{24}$ = +147° (*c* 1.0, MeOH); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.92 (s, 1H), 5.28 (s, 1H), 5.00 (s, 1H), 4.94 (d, *J* = 17.9 Hz, 1H) 4.81 (d, *J* = 17.9 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.29 (br s, 1H), 4.20–4.07 (m, 1H), 3.72 (d, *J* = 12.0 Hz, 1H), 3.00–2.85 (m, 1H), 2.25–2.05 (m, 2H); 2.05–1.10 (m, 16 H), 1.38 (s, 3H), 1.31 (s, 3H), 0.96 (s, 3H), 0.91 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (CD_3OD, 75 MHz) δ 176.04, 175.96, 116.9, 100.6, 83.7, 74.6, 74.3, 68.3, 67.3, 66.8, 60.9, 50.1, 49.2, 47.9, 47.8, 46.8, 40.8, 37.9, 36.6, 33.0, 32.4, 26.7, 25.2, 24.1, 23.1, 22.9, 17.7, 17.0, –5.7, –5.9; IR (film) 3447, 2931, 1756, 1744, 1634, 1378, 1234, 1036 cm^{-1}; HRMS (LSIMS) *m/z* 593.3507 (593.3510 calcd for $C_{32}H_{53}O_8Si$, M+H).

Compound (**11**) could be converted back to ouabagenin. An solution of **11** (10.0 mg, 0.169 mmol), HCl (5.0 N, 1 mL) and MeOH (4 mL) and maintained at rt for 4 h. The solution was then concentrated and the residue was azeotroped with toluene and dried (1 mm, rt) to a constant weight. The resulting solid was recrystallized from hot EtOH to furnish 4.5 mg (72%) of ouabagenin.

1,19-Acetonide-3-(*tert*-butyldimethylsiloxy)-11-oxoouabagenin (12). A suspension of freshly prepared Dess-Martin periodinane (14.0 g, 33.0 mmol),[15] **11** (12.0 g, 20.2 mmol) and CH_2Cl_2 (200 mL) was maintained for 5 h at rt. The colorless suspension was then poured into a saturated aqueous solution of $NaHCO_3$ (600 mL) and vigrously stirred for 5 min. The layers were separated and the aqueous layer was

further extracted with EtOAc (3 × 200 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to provide a solid that was purified by flash chromatography (1:1 EtOAc-hexanes to 100% EtOAc) to furnish 10.1 g (83%) of **12**: $[\alpha]_D^{24}$ = +21.5° $[\alpha]_{577}^{24}$ = +33.5°, $[\alpha]_{546}^{24}$ = +34.5°, $[\alpha]_{435}^{24}$ = +51.3°, $[\alpha]_{405}^{24}$ = +52.0° (*c* 1.4, EtOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.86 (s, 1H), 5.01 (s, 1H), 4.77 (br s, 2H), 4.57 (br s, 1H) 4.39 (d, *J* = 11.9 Hz, 1H), 4.22 (s, 1H), 3.81 (d, *J* = 11.9 Hz, 1H), 4.20–4.07 (m, 1H), 3.72 (d, *J* = 12.0 Hz, 1H), 3.00–2.85 (m, 1H). 2.25–2.05 (m, 2H); 2.05-1.10 (m, 13H), 1.38 (s, 3H), 1.31 (s, 3H), 0.96 (s, 3H), 0.91 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.9, 174.4, 171.2, 118.1, 100.4, 83.3, 73.8, 73.3, 67.6, 65.8, 60.5, 54.8, 52.3, 52.0, 49.0, 45.2, 42.9, 38.2, 36.4, 34.5, 33.1, 26.8, 26.0, 25.3, 23.7, 23.6, 19.4, 18.2, –4.5, –4.8; IR (film) 3464, 2935, 2867, 1755, 1743, 1624, 1378, 1257, 1222, 1036 cm^{-1}; HRMS (LSIMS) *m/z* 591.3354 (591.3353 calcd for $C_{32}H_{51}O_8Si$, M+H). Recrystallization of **12** from hot toluene provided large colorless prisms (mp 205 °C) that were suitable for single crystal X-Ray crystallographic analysis.

Compound (**12**) could be converted back to **11** by reduction with triisobutylaluminum. Triisobutylaluminum (1.0 M in PhMe, 0.40 mL) was added dropwise to a solution of **12** (20 mg, 0.034 mmol) and toluene (1 mL) at rt. The resulting solution was maintained at rt for 6 h, then poured into a saturated aqueous NH_4Cl solution (50 mL) and extracted with EtOAc (3 × 100 mL). The organic extracts were combined, dried (Na2SO4), and concentrated to afford a residue that was purified by **flash *chr*omatography (100% EtOAc to 10:1 EtOAc-MeOH) to provide 11 (17 mg, 84%).**

1,19-Acetonide-3-(*tert*-butyldimethylsiloxy)-11β-hydroxyouabagenin (13). Sodium borohydride (500 mg, 13.1 mmol) was added portionwise to a 0 °C solution of **12** (5.0 g, 8.5 mmol) and MeOH (50 mL). After 1 h, the reaction was poured into saturated aqueous NH_4Cl (200 mL) and extracted with EtOAc (3 × 200 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated to furnish **13** as a thick colorless foam: $[\alpha]_D^{24}$= +46.3° $[\alpha]_{577}^{24}$ = +47.4°, $[\alpha]_{546}^{24}$ = +59.5°, $[\alpha]_{435}^{24}$ = +59.9°, $[\alpha]_{405}^{24}$ = +77.4° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.89 (s, 1H), 5.21 (s, 1H), 4.93 (d, J = 18.2, 1H), 4.83 (d, *J* = 18.2, 1H), 4.63 (d, *J* = 11.3 Hz, 1H), 4.35–4.20 (m, 3H), 4.05 (d, *J* = 11.3 Hz, 1H), 2.78–2.71 (m, 1H), 2.15–2.02 (m, 1H); 2.00–1.60 (m, 13H), 1.52–1.25 (m, 3H), 1.36 (s, 3H), 1.29 (s, 3H), 1.13 (s, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.8, 175.6, 118.4, 102.0, 86.0, 77.2,

74.0, 73.1, 67.8, 66.9, 65.9, 59.8, 51.4, 49.4, 47.0, 46.2, 44.6, 37.0, 35.8, 33.2, 33.0, 27.2, 25.9, 24.6, 23.8, 23.4, 18.5, 18.1, –4.6, –4.7; IR (film) 3375, 2934, 2870, 1750, 1743, 1630, 1374, 1223, 1086 cm^{-1}; HRMS (LSIMS) *m/z* 593.3505 (593.3510 calcd for $C_{32}H_{53}O_8Si$, M+H).

1,19-Acetonide-3-(*tert*-butyldimethylsiloxy)-11β-(trimethylsiloxy)ouabagenin (14). Compound (**13**) (100 mg, 0.17 mmol), 1-(trimethylsilyl)imidazole (0.5 mL, 5.2 mmol) and THF (0.5 mL) were combined and heated at 50 °C in a sealed tube for 12 h. Upon cooling to rt, the reaction was poured into brine (100 mL) and extracted with EtOAc (3 × 100 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated to furnish crude **14**, which was used without further purification: ^1H NMR ($CDCl_3$, 500 MHz) δ 5.88 (s, 1H), 5.00 (s, 1H), 4.96 (d, *J* = 17.5 Hz, 1H), 4.78 (d, *J* = 17.5 Hz, 1H), 4.29–4.20 (m, 4H), 2.70 (dd, *J* = 11.0, 4.5 Hz, 1H), 2.10–1.63 (m, 16H), 1.39-1.14 (m, 2H), 1.36 (s, 3H), 1.27 (s, 3H), 1.23 (s, 3H), 0.90 (s, 9H), 0.19 (s, 9H), 0.08-0.07 (m, 6H); HRMS (LSIMS) *m/z* 665.3903 (665.3904 calcd for $C_{35}H_{61}O_8Si_2$, M+H).

To verify the position of the TMS protecting group, **14** was converted to its $\Delta^{14,15}$ congener using the elimination conditions described for the preparation of **15**. Spectroscopic data for the $\Delta^{14,15}$ analog: $[\alpha]_D^{24}$ = +55.3°; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.90 (s, 1H), 5.31 (br s, 1H), 5.25 (s, 1H), 5.03 (s, 1H), 4.78 (d, *J* = 18.0, 1H), 4.72 (d, *J* = 18.0, 1H), 4.52 (s, 1H), 4.32–4.20 (m, 4H), 2.67–2.60 (m, 1H), 2.53–2.40 (m, 3H), 2.20–1.10 (m, 10H), 1.38 (s, 3H), 1.30 (s, 3H), 1.08 (d, *J* = 13.0, 1H), 1.02 (s, 3H), 0.91 (s, 9H), 0.19 (s, 9H), 0.08 (br s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.3, 170.6, 155.4, 118.2, 116.8, 100.8, 73.7, 68.2, 67.8, 66.7, 58.2, 54.4, 48.9, 48.2, 47.2, 46.0, 37.5, 34.8, 33.3, 33.0, 29.2, 26.6, 26.0, 25.7, 23.6, 22.3, 18.2, 1.3, –4.5, –4.7; IR (film) 3346, 1777, 1752, 1610 cm^{-1}; LRMS (ES TOF) *m/z* 669.4 (669.4 calcd for $C_{35}H_{58}O_7NaSi_2$, M+Na). DEPT 90 carbon experiment shows resonances at 68.2, 67.8, 66.7 corresponding to three $R_2\underline{C}HOR$ carbons (C1, C3, and C11). DEPT 135 carbon experiment shows two negative resonances at 73.8 and 58.2 corresponding to two $R\underline{C}H_2OR'$ carbons (C19 and C24).

1,19-Acetonide-3-(*tert*-butyldimethylsiloxy)-11β-hydroxy-14,15-dehydrooouabagenin (15). Distilled methanesulfonyl chloride (MsCl, 0.3 mL, 0.26 mmol) was added dropwise to a solution of **13** (50 mg, 0.084 mmol), Et_3N (2.0 mL, 1.52 mmol) and CH_2Cl_2 (10 mL) at a rate that heated the solution to *ca.* 35

°C. After 10 min, an additional aliquot of MsCl (0.3 mL, 0.26 mmol) was added in similar fashion. The dark red solution, which deposited a yellow precipitate, was maintained for 1 h at rt. The suspension was poured into saturated aqueous $NaHCO_3$ and the resulting mixture was extracted with EtOAc. The organic extracts were combined, dried ($MgSO_4$), and concentrated to a afford a crude residue that was purified by flash chromatography (2:1 EtOAc-hexanes) to furnish **15** (36 mg, 75%) as a thick oil: $[\alpha]_D^{24}$ = –4.2°, $[\alpha]_{577}^{24}$ = –6.3°, $[\alpha]_{546}^{24}$ = –20.1° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.90 (s, 1H), 5.31 (br s, 1H), 5.25 (s, 1H), 4.86 (dd, *J* = 17.4, 1.7 Hz, 1H), 4.72 (d, *J* = 17.4, 1H), 4.65 (d, *J* = 11.9 Hz, 1H), 4.47 (br s, 1H), 4.32–4.26 (m, 2H), 4.13 (d, *J* = 11.3 Hz, 1H), 4.10–4.04 (m, 1H), 3.16 (s, 1H), 2.72–2.70 (m, 1H), 2.50–2.43 (m, 2H), 2.21 (dd, *J* = 13.4, 2.8 Hz, 1H) 2.05–1.90 (m, 2H), 1.78–1.72 (m, 1H), 1.68–1.61 (m, 1H), 1.53–1.28 (m, 5H), 1.33 (s, 3H), 1.26 (s, 3H), 1.16 (d, *J* = 12.7, 1H), 1.05 (s, 3H), 0.91 (s, 9H), 0.08 (br s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.3, 170.7, 153.5, 118.4, 116.9, 102.1, 73.8, 73.2, 67.9, 67.2, 66.0, 59.4, 53.8, 48.0, 47.1, 47.0, 37.0, 35.7, 33.7, 33.0, 32.0, 29.5, 26.2, 26.0, 24.6, 23.8, 20.8, 18.1, –4.5, –4.7; IR (film) 3478, 2929, 1781, 1751, 1630, 1380, 1223, 1173, 1076 cm^{-1}; HRMS (LSIMS) *m/z* 575.3398 (575.3403 calcd for $C_{32}H_{51}O_7Si$, M+H). DEPT 90 carbon experiment shows resonances at 67.9, 67.2, 66.0 corresponding to three $R_2\underline{C}HOR$ carbons (C1, C3, and C11). DEPT 135 carbon experiment shows two negative resonances at 73.8 and 59.4 corresponding to two $R\underline{C}H_2OR'$ carbons (C19 and C24).

Compound (**15**) was converted back to compound (**13**) by means of bromohydrin formation and subsequent debromination. A solution of *N*-bromosuccinamide (20.0 mg, 0.11 mmol) and H_2O–DME (1:20, 0.5 mL) was added dropwise to a solution of **15** (10.0 mg, 0.26 mmol) and DME (7 mL) at rt. After 30 min, the mixture was poured into a saturated aqueous NH_4Cl (50 mL) and the resulting mixture was vigorously shaken. This mixture was extracted with EtOAc (3 × 10 mL) and the organic extract was washed with brine (10 mL), dried (Na_2SO_4) and concentrated to furnish the extremely base-sensitive bromohydrin, which was taken on without purification. Spectoscopic evidence for the intermediate bromohydrin: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.90 (s, 1H), 5.29 (s, 1H), 4.78 (m, 2H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.43–4.21 (m, 3H), 4.05 (d, *J* = 12.0 Hz, 1H), 2.40–1.20 (m, 17 H), 1.37 (s, 3H), 1.29 (s, 3H), 1.15 (s, 3H), 0.92 (s, 9H), 0.10 (m, 6H); LRMS (ES TOF) *m/z* 693.2 (693.2, calcd for $C_{32}H_{51}O_8BrNaSi^{79}$, M+Na).

Freshly prepared Bu_3SnH (0.10 mL, 0.37 mmol) was added to a solution of the bromohydrin, AIBN (10.0 mg, 0.061 mmol) and benzene (1.0 mL). The resulting solution was maintained at rt for 24 h under a 200 W light source. The reaction mixture was quenched by addition of brine (10 mL) and extracted with EtOAc (3 × 10 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated to furnish a residue that was purified by flash chromatography (1:1 EtOAc-hexanes) to provide 5.7 mg of **13** (55% from **15**).

1,19-Acetonide-3-(*tert*-butyldimethylsiloxy)-11-oxo-14-(trimethylsiloxy)ouabagenin (16). A solution of 1-(trimethylsilyl)imadazole (0.60 mL, 2.5 mmol), **12** (123 mg, 0.21 mmol) and THF (1.0 mL) was heated in a resealable tube at 90 °C for 48 h (until complete consumption of starting material). The reaction mixture was allowed to cool, poured into a saturated aqueous brine solution (100 mL) and extracted with EtOAc (3 × 100 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated to afford a yellow residue that was purified by flash chromatography (1:3 EtOAc-hexanes) to provide a colorless foam **16** (116 mg, 84%): $[\alpha]_D^{24}$ = +12.2°, $[\alpha]_{577}^{24}$ = +18.0°, $[\alpha]_{546}^{24}$ = +23.2° (*c* 0.3, MeOH); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.89 (br s, 1H), 5.14 (s, 1H), 5.25(s, 1H), 4.83 (dd, *J* = 17.7, 1.8 Hz, 1H), 4.72 (dd, *J* = 17.7, 1.0 Hz, 1H), 4.61–4.59 (m, 1H), 4.55 (d, *J* = 12.3 Hz, 1H), 4.30 (br s, 1H), 3.75 (d, *J* = 12.3 Hz, 1H), 2.84 (d, *J* = 12.6 Hz, 1H), 2.34 (dd, *J* = 12.6, 5.6 Hz, 1H) 2.17–2.10 (m, 2H), 2.05–1.42 (m, 8H), 1.33 (s, 3H), 1.26 (s, 3H), 1.17–1.00 (m, 1H), 0.94 (s, 9H), 0.89 (s, 3H), 0.22 (s, 9H), 0.10 (br s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 213.2, 173.8, 169.3, 117.8, 101.0, 87.7, 73.6, 73.1, 67.8, 65.6, 60.4, 54.1, 52.3, 51.6, 47.8, 46.8, 44.3, 38.0, 37.0, 34.4, 33.0, 26.9, 26.0, 24.4, 24.0, 23.2, 22.0, 18.2, 3.2, –4.5, –4.7; IR (film) 3488, 2953, 2856, 1783, 1752, 1701, 1635, 1458, 1378, 1294, 1252, 1134, 1053 cm^{-1}; HRMS (LSIMS) *m/z* 663.3751 (663.3748 calcd for $C_{35}H_{59}O_8Si_2$, M+H).

1,19-Acetonide-3-(*tert*-butyldimethylsiloxy)-11-β-hydroxy-14-(trimethylsiloxy)ouabagenin (17). Sodium borohydride (50 mg, 1.3 mmol) was added portionwise to a 0 °C solution of **16** (100 mg, 0.15 mmol) and MeOH (8.0 mL). After 5 min, the solution was allowed to warm to rt and was maintained at rt for 1.0 h. The mixture was then poured into a saturated aqueous NH_4Cl (100 mL) and was extracted with EtOAc (3 × 100 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated to afford the intermediate C11 alcohol, which was used without further purification. This intermediate was dehydrated

by the procedure described for the conversion of **13** to **15**, and the resulting product was purified by flash chromatography (1:1 EtOAc-hexanes) to furnish 74 mg of **17** (76%) as a colorless foam: $[\alpha]_D^{24}$ = +47.4° $[\alpha]_{577}^{24}$ = +48.2°, $[\alpha]_{546}^{24}$ = +53.8°, $[\alpha]_{435}^{24}$ = +95.5°, $[\alpha]_{405}^{24}$ = +105° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.88 (s, 1H), 5.33 (s, 1H), 5.02 (s, 1H), 4.81 (m, 2H), 4.54 (d, *J* = 11.6, 1H), 4.47 (br s, 1H), 4.27 (br s, 1H), 3.52 (d, *J* = 11.6, 1H), 2.72–2.70 (m, 1H), 2.21–1.72 (m, 11H), 1.62–1.57 (m, 2H), 1.39 (s, 3H), 1.37 (s, 3H), 1.32–1.18 (m, 2H), 0.92 (s, 9H), 0.90 (s, 3H), 0.17 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.7, 174.0, 140.0, 117.7, 117.3, 99.9, 89.5, 74.2, 74.0, 68.5, 67.4, 65.3, 49.5, 49.3, 47.5, 41.9, 41.3, 38.9, 36.1, 35.1, 33.9, 26.9, 26.0, 25.7, 25.2, 23.0, 18.2, 17.6, 3.11, –4.5, –4.7; IR (film) 3490, 2953, 2858, 1783, 1754, 1636, 1471, 1368, 1252 cm^{-1}; HRMS (ES TOF) *m/z* 669.3627 (669.3619 calcd for $C_{35}H_{58}O_7NaSi_2$, M+Na). DEPT 90 carbon experiment shows resonances at 68.6 and 67.4 corresponding to two $R_2\underline{C}HOR$ carbons (C1 and C3).

Aldehyde (19). Ozone was bubbled through a –78 °C solution of **12** (1.0 g, 1.69 mmol) and EtOAc (130 mL). Once the deep blue color persisted, excess ozone was removed by bubbling N_2 through the solution until the solution became nearly colorless. Zinc dust (6.0 g, 91.7 mmol) and AcOH (5.0 mL, 110 mmol) were added and the stirred suspension was allowed to warm to rt. After 2 h, the suspension was filtered through a pad of Celite (wetted with EtOAc) and the pad was washed with additional EtOAc (200 mL). The eluent was washed with brine (100 mL), dried (Na_2SO_4) and concentrated to afford α-hydroxy ketone (**18**), which was used without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.91 (s, 1H), 4.73–4.71 (m, 1H), 4.38 (d, *J* = 12.5 Hz, 1H), 4.34 (s, 1H), 4.30 (s, 1H), 4.25 (br s, 1H), 3.95 (d, *J* = 12.5, 1H), 2.50 (dd, J= 7.5, 4.0 Hz, 1H), 2.37 (d, *J* = 10 Hz, 1H), 2.18–1.87 (m, 10H), 1.45 (s, 3H), 1.71–1.55 (m, 5H), 1.37 (s, 3H), 1.25 (s, 3H), 1.32–1.15 (m, 2H), 0.93 (s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 215.9, 208.0, 99.9, 83.6, 73.1, 70.5, 67.3, 66.2, 60.7, 57.0, 55.1, 52.6, 51.9, 43.4, 42.0, 38.3, 35.8, 34.6, 33.5, 30.3, 26.0, 25.3, 24.4, 23.9, 18.5, 17.1, –4.5, –4.7; IR (film) 3470, 2931, 2859, 1712, 1466, 1380 cm^{-1}.

The crude α-hydroxy ketone was dissolved in MeOH (75 mL) and $NaBH_4$ (1.0 g, 26 mmol) was added portionwise at rt. The resulting solution was maintained for 0.5 h then concentrated. The solid residue was taken up in EtOAc (300 mL) and washed with brine (3 x 50 mL). The organic layer was dried

(Na_2SO_4) and concentrated to furnish an oil that was subsequently dissolved in benzene (100 mL) and $Pb(OAc)_4$ (1.0 g, 2.3 mmol) was added. The resulting red solution was maintained at rt for 2.0 h and then concentrated. The solid residue was applied directly to a flash chromatography column with 5 mL of CH_2Cl_2 and eluted with 1:1 EtOAc-hexanes to furnish **19** as a thick colorless foam (502 mg, 55%): $[\alpha]_D^{24}$ = +80.5°, $[\alpha]_{546}^{24}$ = +133° (*c* 0.3, $CDCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.76 (d, *J* = 5.0 Hz, 1H), 5.21 (br s, 1H), 4.65 (d, *J* = 14.5, 1H), 4.32–4.22 (m, 3H), 4.08 (d, *J* = 14.5 Hz, 1H), 2.41–2.37 (m, 1H), 2.23–2.02 (m, 1H), 2.00–1.30 (m, 16H), 1.40 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H), 1.13–1.07 (m, 1H), 0.92 (s, 9H), 0.11–0.10 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.8, 102.0, 85.6, 73,1, 67.8, 67.0, 66.0, 62.3, 60.0, 50.3, 47.0, 44.6, 44.5, 37.0, 36.2, 35.8, 33.3, 33.0, 26.0, 24.6, 23.8, 23.4, 20.5, 18.1, 18.0, –4.6, –4.7; IR (film) 3476, 2931, 2858, 1711, 1464, 1223 cm^{-1}; HRMS (LSIMS) *m/z* 539.3410 (539.3404 calcd for $C_{29}H_{51}O_7Si$, M+H).

Nitrile (20). A solution of **19** (200 mg, 0.37 mmol), NH_2OH•HCl (100 mg, 1.5 mmol), NaOAc (220 mg, 1.6 mmol) and EtOH (4 mL) was maintained for 1 h at rt and then concentrated. The resulting residue was dissolved in H_2O (30 mL) and extracted with CH_2Cl_2 (3 x 150 mL). The combined organic extracts were dried ($MgSO_4$), and concentrated. The resulting oxime was redissolved in CH_2Cl_2 (30 mL) and 1,1'-carbonyldiimidazole (200 mg, 1.2 mmol) was added at rt. The reaction was maintained at rt for 12 h, saturated aqueous NH_4Cl was added, and the mixture was extracted with EtOAc (3 x 150 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to a residue that was purified by flash chromatography (1:3 EtOAc-hexanes) to furnish **20** (149 mg, 75%) as a colorless foam: $[\alpha]_D^{24}$ = +39.6° $[\alpha]_{577}^{24}$ = +39.6°, $[\alpha]_{546}^{24}$ = +46.7°, $[\alpha]_{435}^{24}$ = +72.9°, $[\alpha]_{405}^{24}$ = +82.8° (*c* 2.5, MeOH); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.22 (s, 1H), 4.64 (d, *J* = 11.9, 1H), 4.52–4.50 (m, 1H), 4.34 (br s, 1H), 4.28 (br s, 1H), 4.24 (br s, 1H), 4.22 (br s, 1H), 4.10 (d, *J* = 11.9, 1H), 2.63 (dd, *J* = 9.5, 3.9 Hz, 1H), 2.29–2.11 (m, 2H), 2.03–1.21 (m, 8H), 1.54 (s, 3H), 1.39 (s, 3H), 1.32 (s, 3H), 1.17–1.03 (m, 1H), 0.91 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 122.9, 102.1, 85.7, 73.1, 67.8, 66.5, 65.9, 59.9, 48.3, 47.0, 44.6, 43.0, 41.0, 37.0, 36.4, 35.8, 33.0, 32.5, 26.0, 25.8, 24.6, 23.8, 23.3, 18.8, 18.2, –4.6, –4.7; IR (film) 3475, 2930, 2857, 2240, 1464, 1370, 1223 cm^{-1}; HRMS (LSIMS) *m/z* 536.3411 (535.3407 calcd for $C_{29}H_{49}NO_6Si$, M+H).

Aldehyde (21). Compound (**21**) was accessed from **19** (502 mg, 0.93 mmol) using the dehydration procedure described for the preparation of **15**. The resulting crude product was purified by flash chromatography (1:1 EtOAc-hexanes) to furnish 388 mg (80%) of **21**: $[\alpha]_D^{24}$ = –20.0°, $[\alpha]_{577}^{24}$ = –48.0°, $[\alpha]_{405}^{24}$ = –72.0° (*c* 0.1, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.86 (d, *J* = 2.0 Hz, 1H), 5.24 (s, 1H), 5.21 (s, 1H), 4.64 (d, *J* = 15.0, 1H), 4.67 (s, 1H), 4.29–4.25 (m, 2H), 4.13 (d, *J* = 15.0, 1H), 4.09 (br s, 1H), 2.78–2.72 (m 1H), 2.69–2.64 (m, 1H), 2.50 (br s, 1H), 2.46 (dd, *J* = 17.0, 3.5 Hz, 1H), 2.40–2.32 (m, 1H), 2.06–1.87 (m, 3H), 1.80–1.15 (s, 7H), 1.33 (s, 3H), 1.27 (s, 3H), 1.19 (s, 3H), 0.91 (s, 9H), 0.09 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.1, 152.0, 117.7, 101.5, 72.7, 67.4, 66.9, 65.4, 64.6, 59.0, 48.0, 47.4, 47.0, 46.5, 36.4, 35.2, 32.5, 29.4, 28.5, 25.7, 25.4, 24.0, 23.2, 21.6, 17.8, –5.1, –5.3; IR (film) 3479, 2929, 1719, 1414, 1223 cm^{-1}; HRMS (LSIMS) *m/z* 522.3292 (522.3298 calcd for $C_{29}H_{48}O_6Si$, M+H).

Nitrile (22). Compound (**21**) (100 mg, 0.19 mmol) was converted to **22** using the general procedure described for the conversion of **19** to **20**. The resulting crude product was purified by flash chromatography (1:3 hexanes-EtOAc) to give **22** (72 mg, 72%) as a colorless solid: $[\alpha]_D^{24}$ = +95.2° $[\alpha]_{577}^{24}$ = +116°, $[\alpha]_{546}^{24}$ = +130°, $[\alpha]_{435}^{24}$ = +181°, $[\alpha]_{405}^{24}$ = +233° (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.25 (s, 1H), 5.21 (s, 1H), 4.65 (d, *J* = 10.5, 1H), 4.64 (s, 1H), 4.28–4.25 (m, 2H), 4.13 (d, *J* = 10.5 Hz, 1H), 4.11 (s, 1H), 2.67–2.65 (m, 2H), 2.50–2.40 (m, 1H), 2.37 (dd, J = 13.7, 2.8 Hz, 1H), 2.05–1.85 (m, 3H), 1.78–1.55 (m, 2H), 1.53–1.23 (m, 5H), 1.43 (s, 3H), 1.40 (s, 3H), 1.34 (s, 3H), 1.17–1.06 (m, 1H), 0.91 (s, 9H), 0.13–0.09 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.0, 121.0, 117.3, 102.1, 73.2, 67.9, 67.0, 66.0, 59.4, 48.0, 47.3, 47.04, 47.01, 42.9, 37.0, 35.6, 34.8, 33.0, 29.6, 26.2, 26.0, 24.6, 23.8, 22.3, 18.1, –4.6, –4.7; IR (film) 3478, 2931, 2238, 1464, 1380, 1256 cm^{-1}; HRMS (LSIMS) *m/z* 536.3411 (518.3302 calcd for $C_{29}H_{48}NO_5Si$, M+H). Anal. Calcd for $C_{29}H_{47}NO_5Si$: C, 67.27; H, 9.15; N, 2.71. Found: C, 67.28; H, 9.34; N, 2.71. DEPT 90 carbon experiment shows resonances at 67.9, 67.0, 66.0 corresponding to three $R_2\underline{C}HOR'$ carbons (C1, C3, and C11).

A sample of **22** (20 mg, 0.039 mmol) was dissolved in EtOAc (0.4 mL) and diluted with hexanes (5 mL). The resulting solution was allowed to stand at rt for 24 h to furnish colorless thin prisms (mp 179–180 °C) suitable for single crystal X-Ray analysis.

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