CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.200800429

Total Synthesis of Ouabagenin and Ouabain

Maddi Sridhar Reddy, Hongxing Zhang, Serge Phoenix, and Pierre Deslongchamps*[a]

Abstract: A full account of the total synthesis of ouabagenin and ouabain is described. A highly stereocontrolled anionic cycloaddition for the rapid construction of the basic steroid skeleton is a pivotal conversion for the whole strategy. A careful study was needed to establish the order and the sequence of functional group manipulations. Specific conformational features of the ouabain skeleton allowed us to overcome a few stereochemical problems. Degradation studies on ouabain provided an ultimate proof for a key intermediate, which is used as a relay. Late stage butenolide formation and glycosidation yielded ouabain.

Keywords: cycloaddition · glycosides · glycosylation · steroids · total synthesis

Introduction

Cardioactive glycosides, so named for their dramatic effect on the heart, have been used by indigenous populations in Africa and Asia as dart poisons and have also found extensive use in modern medicine for the treatment of congestive heart failure.[1] They are a large group of steroids, which possess a sugar moiety at the 3β position and have been isolated from both plant and animal sources.[2] Ouabain (**1**), digoxin (**2**), and digitoxin (**3**), the representatives of this class, and their aglycones (ouabagenin (**1b**), digoxigenin (**2b**), and digitoxigenin (**3b**), respectively) are known as cardenolides that differ from other steroids with a β-oriented butenolide ring at C17, an A/B and C/D *cis* ring fusion and a β tertiary hydroxyl group at C14 (Figure 1).

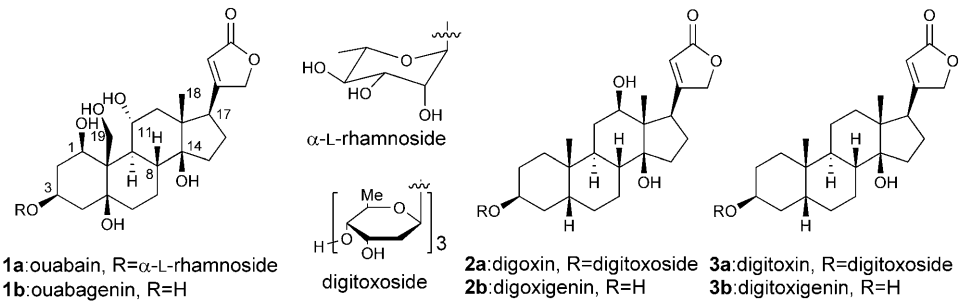


Figure 1. Structure of some cardenolides.

Ouabain (**1**), first isolated from the roots and the bark of the African ouabio tree (*Acokanthera ouabaio*) by Arnaud in 1888,[3] has received considerable attention because it was discovered that an ouabain-like compound occurs naturally in mammals and acts as an endogenous digitalis as proposed by Szent-Gyorgyi.[4] After some debate, it was established that the endogenous and plant derived ouabain were in fact identical.[5]

Ouabagenin (**1b**), the aglycone of ouabain, was isolated for the first time in 1942 by Mannich and Siewert.[6] Ouabain, along with its aglycone ouabagenin, has posed a formidable synthetic challenge until now, owing to their high propensity for oxygenation. Although a lot of progress towards the construction of ouabain has been made recently,[7–9] no total synthesis has been reported. Our foray into this field has been based on a hypothesis that the polyanionic cyclization (double Michael addition followed by aldol condensation) methodology, developed by our research group,[10] would allow facile access to an appropriately functionalized

[a] Dr. M. S. Reddy, Dr. H. Zhang, Dr. S. Phoenix, Prof. Dr. P. Deslongchamps
Laboratoire de Synthèse Organique
Département de Chimie
Institut de Pharmacologie de Sherbrooke
Université de Sherbrooke
Sherbrooke, Québec J1H 5N4 (Canada)
Fax: (+1) 819-820-6823
E-mail: pierre.deslongchamps@usherbrooke.ca

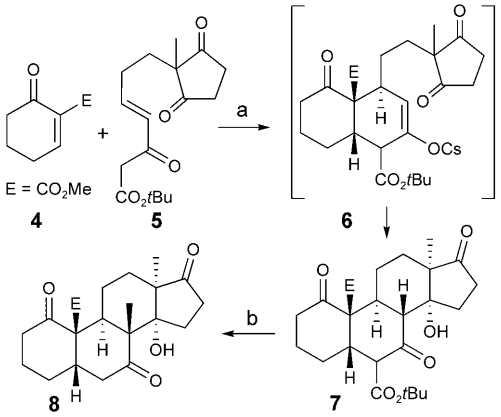
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.200800429.

tetracyclic intermediate with the desired stereochemistry at the ring junctions. Our initial studies[10,11] suggested a promising synthetic route towards 14-β-OH steroidal intermediates and herein we report the full account of the total synthesis of these steroids which we disclosed recently.[12]

Results and Discussion

Earlier Progress

In 1988, our research group reported that under basic conditions, the reaction between cyclohexenone **4** and the enolate of Nazarov reagent **5** affords, after decarboxylation, the tetracyclic compound **8** (through intermediates **6** and **7**) with good diastereoselectivity (Scheme 1).[10a] This tandem

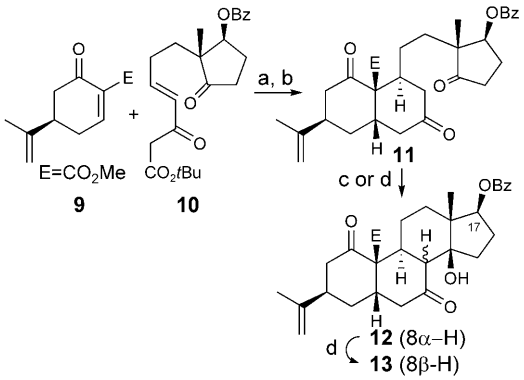


Scheme 1. Synthesis of tetracyclic compound **8** by polyanionic cyclization. a) Cs_2CO_3, $CHCl_3$, RT; b) PTSA, PhH, reflux, 47% (2 steps).

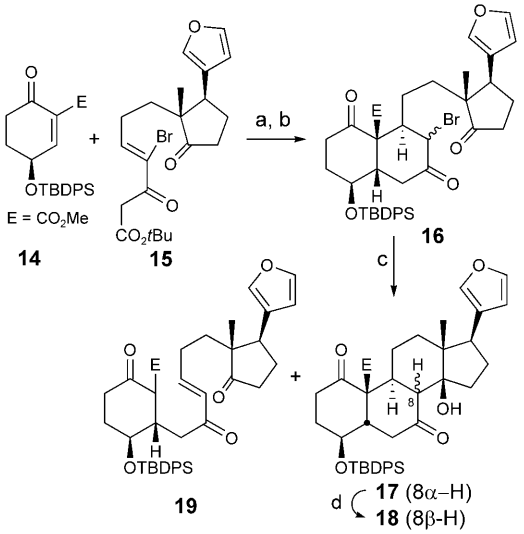
double Michael addition/aldol condensation, the so-called anionic polycyclization, appeared valuable for the synthesis of cardioactive steroids. Ouabain, with the *cis* A/B and C/D, and *trans* B/C ring fusions was identified as a potentially interesting target.

Ouabain and the most naturally occurring cardioactive steroids contain a β-hydroxyl group at C-14, which is opposite to that in the tetracyclic compound **8**. We circumvented this problem by using Nazarov reagent **10**, which contains a β-benzoyloxy group at the *pro*-17 position (steroid numbering) as shown in Scheme 2,[10b] but the diastereoselectivity of the double Michael addition and the yield of aldol condensation were not acceptable.

In order to overcome the two shortcomings, cyclohexenone **14** and brominated Nazarov reagent **15** were developed (Scheme 3)[11a] to obtain the tricyclic bromoketone **16** diastereoselectively. Upon treatment of tricycle **16** with SmI_2 at −20 °C, tetracycle **17** (8α-H) was obtained as the major product in a much improved yield of 63%. The desired isomer **18** (8β-H) was formed in a very low yield of 7%, but was obtained in 90% yield by acidic isomerization of **17**.



Scheme 2. Synthesis of 14β-hydroxy steroid skeleton **13**. a) Cs_2CO_3, $CHCl_3$, RT; b) PTSA, PhH, reflux, 60% (2 steps); c) KHMDS, THF, 25% of **12**; d) Cs_2CO_3, CH_3CN, reflux, 32% of **13** from either **11** or **12**.



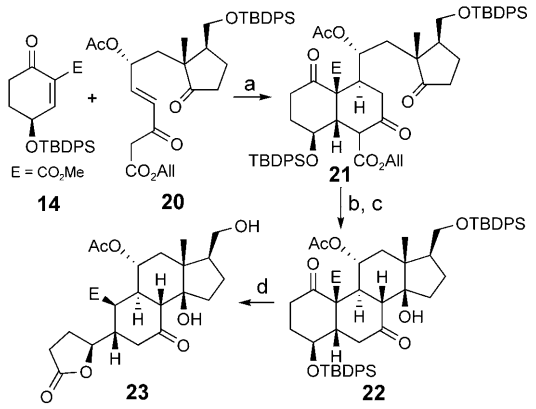
Scheme 3. Preparation of steroid skeleton **18**. a) Cs_2CO_3, CH_2Cl_2, RT; b) PTSA, PhH, reflux, 56% (2 steps); c) SmI_2, THF, −20 °C, 63% (**17**), 7% (**18**), 25% (**19**); d) anhydrous HCl, CH_2Cl_2, 90%.

On the other hand, we discovered that exposure of the Nazarov reagent **20**, which contains an α-acetoxy group at the *pro*-11 position (steroid numbering), to an anionic polycyclization protocol gave tetracyclic compound **22** without difficulty (Scheme 4).[11b] The correct stereochemistry at C8 was directly obtained, and no competition from the retro-Michael degradation was observed. Unfortunately, upon treatment of **22** with TBAF to deprotect the silyl ether, retro-Dieckmann rearrangement occurred to yield g-lactone **23**. Though the synthesis of the skeleton (*cis* A/B and C/D, *trans* B/C) of ouabain was successful, a properly functionalized A-ring at C3 position appeared preferable.

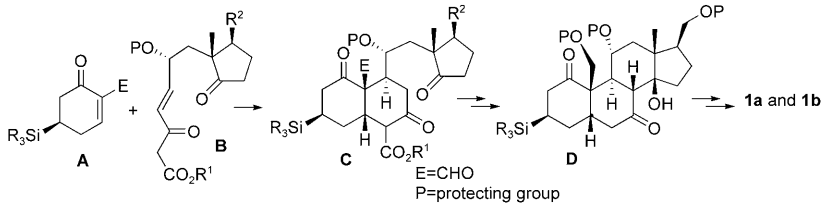
Present Synthetic Planning

Our strategy was based on the initial rapid construction of the densely functionalized tetracycle **D**, through tricycle **C**, from condensation of the chiral building blocks **A** and **B** (Scheme 5). The tetracycle **D**, in principle, contains all the

CHEMISTRY
AN ASIAN JOURNAL



Scheme 4. Accidental preparation of **23**. a) Cs_2CO_3, CH_2Cl_2, RT, 61%; b) $Pd(PPh_3)_4$, morpholine, THF, RT, 71%; c) KHMDS, THF, reflux, 71%; d) TBAF, THF, RT, 85%.



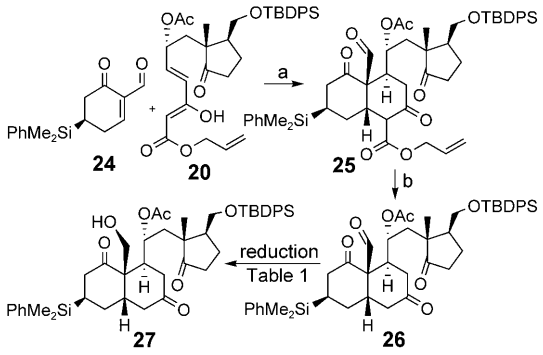
Scheme 5. Synthetic strategy for ouabagenin and ouabain.

required functionalities for a drive towards ouabagenin and, in turn, ouabain. We assumed that the structural feature of the intermediate **D** would allow us to reduce the C1 ketone (steroidal numbering) in a controlled manner. In addition, the C7 ketone could be used to introduce the β-oriented C5 tertiary hydroxyl group. We unambiguously envisioned that the silyl group at C3 would serve as a masked hydroxyl group whereas the substitution at C17 would be the base for the eventual construction of the butenolide ring.

Construction of the Ouabain Steroid Skeleton by Anionic Polycyclization

With the desired substrates in hand for anionic polycyclization, a double Michael addition was performed by treatment of the Nazarov reagent **20**[11b] with cesium carbonate in CH_2Cl_2 at room temperature, followed by cyclohexenone **24**[13,14] at 0°C in 10 min to give the tricyclic product **25** in 85% yield (Scheme 6). Decarboxylation of the allyl ester **25** using tetrakis(triphenylphosphine)palladium(0) and morpholine gave tricycle **26** in 92% yield. Reduction of aldehyde **26** with lithium tris[(3-ethyl-3-pentyl)oxy]aluminohydride,[15] which proved to be superior to sodium borohydride and lithium tri-*tert*-butoxyaluminohydride, afforded alcohol **27** in 89% yield (Table 1).

Protection of alcohol **27** with dimethoxymethane and phosphorus pentoxide yielded the MOM ether **28** in 95% yield which on exposure to KHMDS in THF at reflux gave the desired tetracyclic aldol product **29** in 91% yield (Scheme 7). The acetoxy group at the *pro*-11 position in the

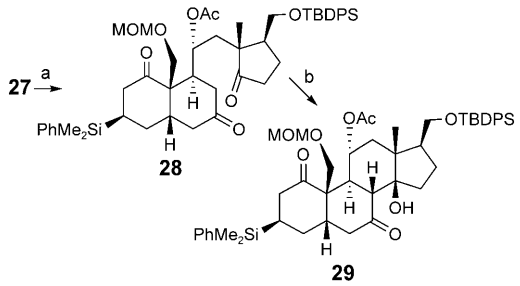


Scheme 6. Preparation of **27**. a) Cs_2CO_3, CH_2Cl_2, 0°C, 85%; b) $Pd(PPh_3)_4$, morpholine, THF, RT, 92%.

α orientation significantly improved the aldol condensation between C8 and C14.[10b,11b] The stereochemistry of the product can be extrapolated from a previous study.[10b,11b] Now that the core tetracycle of ouabain has been constructed in high yield, our next goal was the introduction of the double bond at C5−C6 for the installation of 5β-OH and selective reduction of the carbonyl group at C1.

Table 1. Reduction of aldehyde **26**.

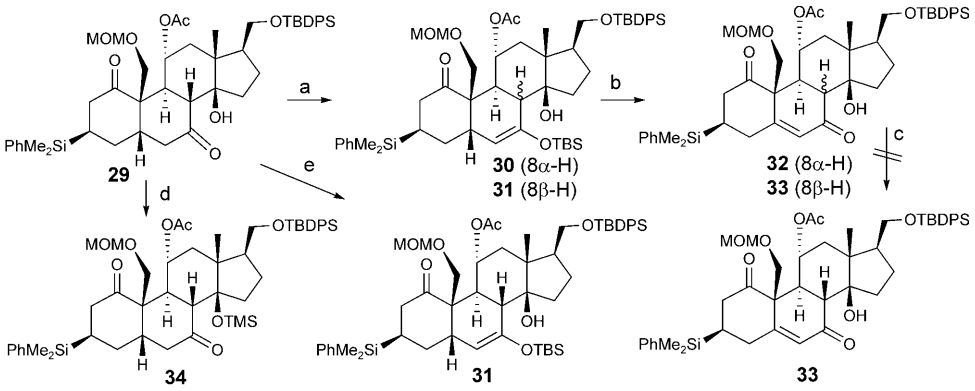
n	Reagents and conditions	Yield
1	$NaBH_4$, EtOH, −20→0°C, 3 h	36%
2	$Li(tBuO)_3AlH$, THF, −78°C, 20 h	84%
3	$Li(Et_3CO)_3AlH$, THF, −78°C, 20 h	89%



Scheme 7. Preparation of **29**. a) $CH_2(OCH_3)_2$, P_2O_5, $CHCl_3$, RT, 95%; b) KHMDS, THF, reflux, 91%.

Attempted Introduction of the Double Bond at Δ^5 and Removal of the C7-oxygen

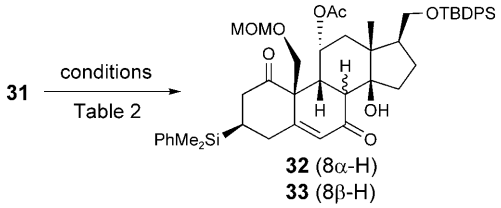
Treatment of diketone **29** with LHMDS and *tert*-butyldimethylsilyl chloride afforded C8 epimeric silyl enol ethers **30** and **31**, which were dehydrosilylated by palladium(II)-promoted oxidation[16] to form a 1:1 mixture of **32** and **33** (Scheme 8). Attempts to get pure **33** by treatment of the mixture with KHMDS in THF, even at elevated tempera-



Scheme 8. Preparation of **31**. a) TBSCl, LHMDS, THF, 0 °C, 64 %; b) $Pd(OAc)_2$, 2,6-di-*tert*-butylpyridine, DMSO, O_2, RT, 68 %; c) KHMDS, THF, reflux; d) TMSOTf, Et_3N, CH_2Cl_2, −10→0 °C, 20 %; e) TBSOTf, Et_3N, CH_2Cl_2, 0 °C→RT, 79 % in 53 % conversion.

ture, were unfruitful. When a less basic condition, namely, trimethylsilyl triflate in the presence of triethylamine, was used, we obtained only the 14-OH protected product **34**. The TMS-protected 14-OH prevented it from further reaction with the C7-carbonyl group. Fortunately, the reaction of diketone **29** with excess *tert*-butyldimethylsilyl triflate[17] and triethylamine in extremely high concentration produced exclusively the silyl enol ether **31** in 79 % yield after 53 % conversion.

The next crucial task was to create a Δ^5 unsaturation from the enol ether moiety. Pd^{II}-promoted oxidation[16] of TBS enol ether **31** resulted in chromatographically separable isomers **32** and **33** (Scheme 9, Table 2). The best ratio of **33** and **32** (7.34:1) was obtained when the oxidation was carried out in weakly acidic conditions.



Scheme 9. Oxidation of **31.** See Table 2.

Table 2. Pd^{II}-promoted oxidation of TBS enol ether **31**.

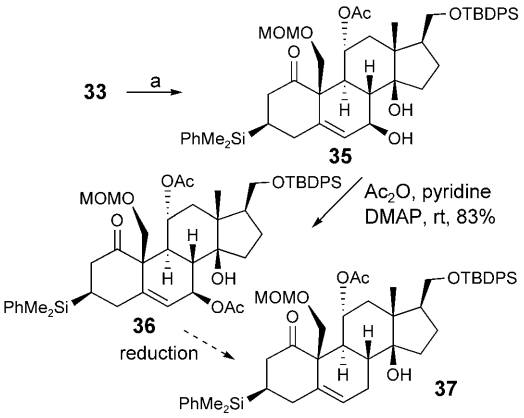
n	Reagents and conditions	**33**:**32**	Conversion	Yield
1	$Pd(OAc)_2$, DMSO, DTBMP*	1.33:1	82 %	67 %
2	$Pd(OAc)_2$, DMSO	2.44:1	75 %	59 %
3	$Pd(OAc)_2$, DMSO, HOAc (0.25 equiv)	7.34:1	40 %	67 %

* DTBMP = 2,6-di-*tert*-butyl-4-methyl pyridine.

With the enone **33** in hand, we then tried to install the 5β-OH through β-selective epoxidation. Reports by Syamala[18] and Salvador[19] demonstrated that highly β-selective epoxidation of Δ^5-unsaturated steroids could be achieved, using the permanganate ion, in high yield.

With the above considerations in mind, we first tried to deoxygenate the unwanted 7-carbonyl group. Reduction of the enone **33** with sodium borohydride in the presence of cerium chloride[20] afforded the allylic alcohol **35** (Scheme 10). Several efforts were made to functionalize the allylic alcohol **35**, which was finally transformed into allylic acetate **36**, but the subsequent deoxygenation to **37** failed.

Chloroaluminohydride[21] was then used for direct deoxygenation of the 7-carbonyl group. The enone **33** was treated with lithium aluminohydride and aluminium chloride in ether at 0 °C to give only alcohol **35**, and not the desired deoxygenated product **37**. Another trial for direct deoxygenation of the 7-carbonyl group of enone **33** by hydrogenation with platinum in HOAc[22] also failed.



Scheme 10. Attempted preparation of **37**. a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH, −30 °C, 91 %.

Reduction of the 1-carbonyl of Diketone 29 Selectively from the α-Face

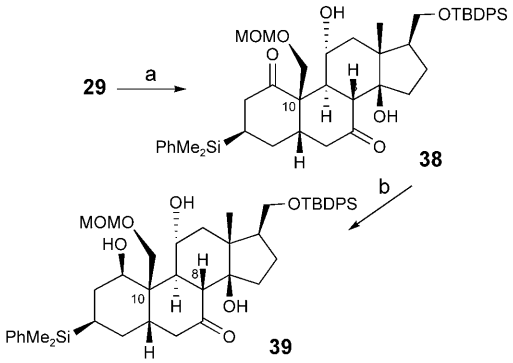
At the beginning of this investigation, we never thought that it was a better choice to reduce the 1-carbonyl before working on the B-ring to establish the 5β-OH. It is evident from our previous studies[11c,23] that with a *cis* A/B junction, the reduction to give a 1β-hydroxyl group appeared problematic. On the other hand, with the Δ^5 double bond, the A- and B-rings of **33** are more flat and therefore it was thought to facilitate the reduction of 1-carbonyl to a 1β-hydroxyl group. However, compound **35** could not be reduced properly by sodium borohydride or lithium borohydride.

Thus, the failure of deoxygenation of the 7-carbonyl, low yield and low conversion for introduction of a double bond

at C5, and apparent difficulty in the reduction of the 1-carbonyl, prompted us to reconsider the reduction of this carbonyl group prior to the introduction of the Δ^5 double bond.

In the case of steroid **29**, it was difficult to reduce the 1-carbonyl whilst leaving the 7-carbonyl untouched. Moreover, it was not easy to obtain the 1β-hydroxyl group by reduction with the *cis*-AB ring fusion as the steroid. The molecular model of steroid **29** shows that 11α-acetoxy and 1-carbonyl are very close and there is no room for the reducing agent to attack the C1-carbonyl from the α-face. On the other hand, literature[24] shows that an ester can be reduced easily with sodium borohydride if there is an oxygen or nitrogen in a neighboring position, since a boron complex could be formed and it could speed up the reduction reaction. In the same way, we anticipated the free 11α-hydroxyl group to aid in the reduction of the 1-carbonyl to a 1β-hydroxyl compound. So we decided to hydrolyze the 11-acetate before the reduction.

Initially, we tried the acetate hydrolysis on TBS enol ether **31**, but failed. Subsequently, we turned to compound **29** (Scheme 11) which was hydrolyzed with potassium carbonate to give alcohol **38** in 96% yield. We were delighted to see that the reduction of diketone **38** with 0.55 equiv of sodium borohydride in EtOH at −78°C afforded alcohol **39** in 96% yield. The result of such a reduction is not surprising but has not, to our knowledge, been reported previously, although it is well known for acyclic compounds.[24] The assignment of the structure of compound **39** was confirmed by the upfield shift of the C10 signal and the unchanged C8 signal in its ^{13}C NMR.



Scheme 11. Reagents and conditions: a) K_2CO_3, THF, MeOH, 96%; b) $NaBH_4$ (0.55 equiv), EtOH, −78°C, 96%.

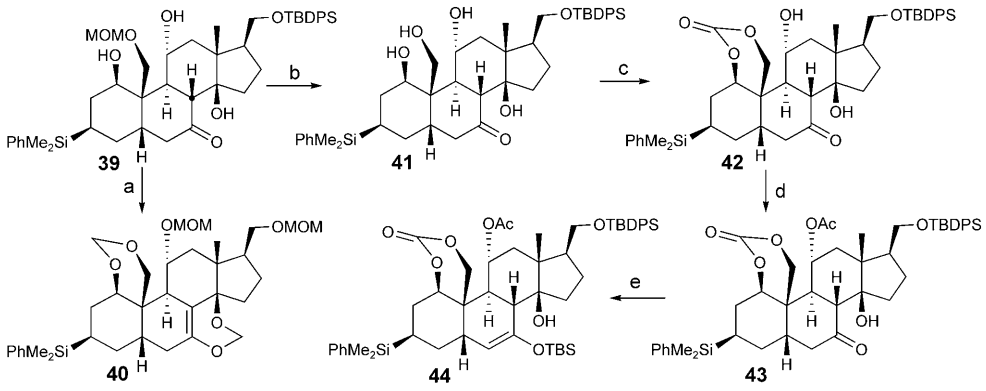
Subsequently, triol **39** was treated with dimethoxymethane and phosphorus pentoxide[25] in chloroform, hoping to form cyclic acetal from 1β-hydroxyl and 19-MOM. However, only unwanted and unexpected diacetal **40** was isolated (Scheme 12). Other conditions known to form cyclic acetal from MOM, such as $P_2O_5/CHCl_3$, PTSA/benzene/reflux,[26] BF_3/CH_2Cl_2,[27] TMSOTf/2,6-lutidine/THF,[28] were tried but also proved to be unfruitful.

Unable to form the cyclic acetal, we attempted the removal of MOM. Compound **39** afforded tetraol **41** in 49% yield when treated with B-bromocatecholborane[29] in CH_2Cl_2 at −78°C. Subsequently, the free hydroxyls at C1 and C19 were selectively protected as a cyclic carbonate in the presence of triphosgene and pyridine[30] to afford **42** in 91% yield, which was then treated with Ac_2O, DMAP, and pyridine to give acetate **43** in 87% yield. Ketone **43** produced silyl enol ether **44** when treated with TBS triflate and Et_3N in CH_2Cl_2 but in impractical yield owing to the decomposing nature of the starting material.

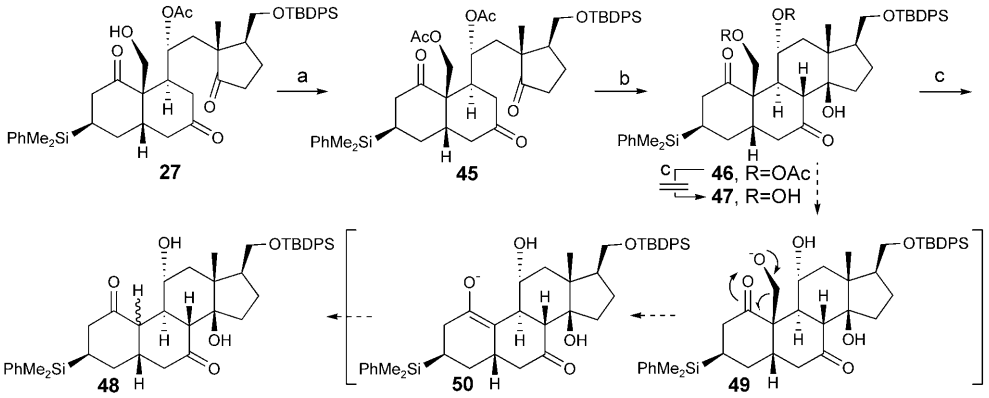
Low yield and nonreproducibility of the removal of MOM and the decomposing nature of the carbonate protected compound convinced us to change the protective group from MOM to acetate, which could later be removed simultaneously with 11-acetate. With this consideration in mind, alcohol **27** was treated with Ac_2O and DMAP in pyridine, followed by aldol condensation of the resulting diacetoxy triketone **45** with KHMDS to give tetracyclic compound **46** (Scheme 13). Unfortunately, hydrolysis of the diacetate **46** did not give **47** but afforded dehydroxymethyl product **48**. The retroaldol mechanism, through **49** and **50**, has been suggested for the reaction.

Formation of 1,11,19-Orthoester

Next, we chose *p*-methoxybenzyl (PMB) ether as the protective group anticipating the intramolecular oxidative formation of cyclic methoxybenzylidene acetal[31] after the reduc-



Scheme 12. Preparation of **44**. a) $CH_2(OCH_3)_2$, P_2O_5, $CHCl_3$, 46%; b) B-bromocatecholborane, CH_2Cl_2, −78°C, 49%; c) triphosgene, pyridine, CH_2Cl_2, −78→0°C, 91%; d) Ac_2O, DMAP, pyridine, RT, 87%, e) TBSOTf, Et_3N, CH_2Cl_2, RT, 10%.



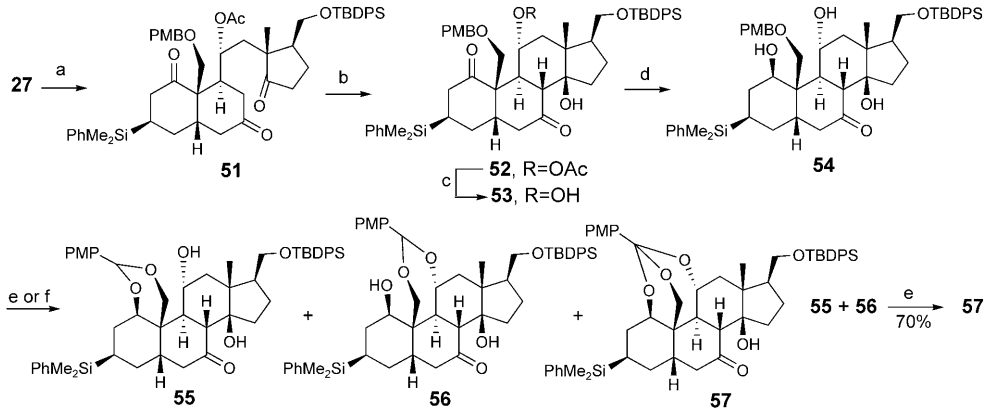
Scheme 13. Accidental preparation of compound **48**. a) Ac_2O, DMAP, pyridine, 98%; b) KHMDS, THF, reflux, 94%; c) K_2CO_3, MeOH, THF, 0°C→RT, 85%.

tion of the 1-carbonyl to its β-hydroxyl function. Alcohol **27** was treated with PMB trichloroacetimidate in the presence of 0.3 mol% trifluoromethanesulfonic acid in ether at 0°C to give PMB protected product **51** (Scheme 14).[32] Following the same protocol described above, a sequence that involves aldol condensation of **51**, followed by hydrolysis of 11-acetate and selective reduction of 1-carbonyl, led, via **53**, to triol **54** in 79% overall yield. With 1-β-hydroxy *p*-methoxybenzyl ether **54** in our hand, we tried Oikawa's conditions[31] for the formation of methoxybenzylidene acetals in order to obtain methoxybenzylidene acetals **55** and **56**. Fortunately, orthoester **57** also formed[33] simultaneously in 17% yield. The result of 1,11,19-orthoester was not surprising. Studies on ouabain[5a,b,34] showed that the A-ring moiety possesses high conformational flexibility and ouabain has a small energy difference between the A-ring chair and twist-boat conformations.

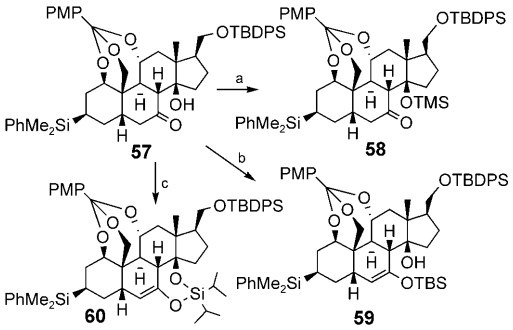
Ouabain has been reported to form labile borate[5a] (1,5,19-tetrahedral borate and 1,11,19-tetrahedral borate) and phosphate complexes[34a] (ouabain 1,5,19-phosphate and 1,11,19-phosphate). Compound **54** has the same steroid skeleton as ouabain with the same 1β-OH, 11α-OH and 19-OH groups. Hence, the A-ring of compound **54** can change from chair to twist-boat conformation to form the orthoester. With the 1,11,19 hydroxyls locked by an orthoester, the C5, C6, and C7 of compound **57** are more sterically accessible as evident from molecular models. Thus, it could be expected that the introduction of a double bond at C5–C6 becomes easier. With this consideration in mind, we optimized this reaction by using 4 equivalents of DDQ and obtained orthoester **57** from **54** in 84% yield. In addition, a mixture of acetals, namely, **55** and **56**, was also obtained in 11% yield and subsequently converted to **57** in 70% yield.

Successful Introduction of the Double Bond at Δ^5 and Introduction of the 5-β-Hydroxyl Group

Following the protocol described above, ketone **57** was treated with TMSOTf and Et_3N and only the 14-hydroxy-protected product **58** was obtained (Scheme 15). Silyl enol ether **59** was successfully produced by treatment of ketone **57** with excess TBSOTf and Et_3N in extremely high concentration. Interestingly, the cyclic silyl enol ether **60** was formed with $(i\text{Pr})_2\text{Si}(\text{OTf})_2$.



Scheme 14. Protection of 19-OH and stereoselective reduction of 1-carbonyl of **27**. a) PMB trichloroacetimidate, TfOH (0.3%), Et_2O, 0°C, 90%; b) KHMDS, THF, reflux, 83%; c) K_2CO_3, MeOH, THF, 98%; d) $NaBH_4$, EtOH, −78°C, 97%; e) DDQ (1.5 equiv), 4 Å molecular sieves, CH_2Cl_2, RT, 20 h, 47% for **55+56**, 17% for **57**; f) DDQ (4 equiv), 4 Å molecular sieves, CH_2Cl_2, RT, 39 h, 84% for **57**, 11% for **55+56**.



Scheme 15. Preparation of silyl enol ether **59**. a) TMSOTf, Et_3N, CH_2Cl_2, RT, 73%; b) TBSOTf, Et_3N, CH_2Cl_2, RT, 90% with 75% conversion; c) $(iPr)_2Si(OTf)_2$, Et_3N, CH_2Cl_2, RT, 90%.

With the desired silyl enol ether **59** in our hands, we began to search for an oxidative method to form the enone **61** (Scheme 16, Table 3). The Pd^{II}-promoted oxidation of **59** according to the procedure described above gave low yield and led to partial epimerization (Table 3, entry 5). The attempted formation of the α-bromo ketone,[35] as a possible precursor to enone **61** by bromination of **59** with NBS, failed (Table 3, entry 3). Selenylation of the TBS enol ether **59** with phenylselenyl chloride[36] or the more active PhSeO-$COCF_3$[37] also proved unfruitful (Table 3, entries 1 and 2).

Eventually, it was found that the desired enone **61** could be obtained from the silyl enol ether **59** by using the modified protocol of Ito et al.[38] Treatment of **59** with DDQ in the presence of $Pd(OAc)_2$ in acetonitrile furnished enone **61** and TBS enol ether **63**, an 8α-H epimer of **59** (Table 3, entry 5). The problem of epimerization at C8 was solved by the addition of 2 equiv of 2,6-di-*tert*-butyl-4-methyl pyridine and the desired enone **61** was obtained from **59** (Table 3, entries 6 and 7). It was later realized that dehydrosilylation of silyl enol ether **59** proceeded smoothly even without the palladium(II) catalyst (Table 3, entry 8).

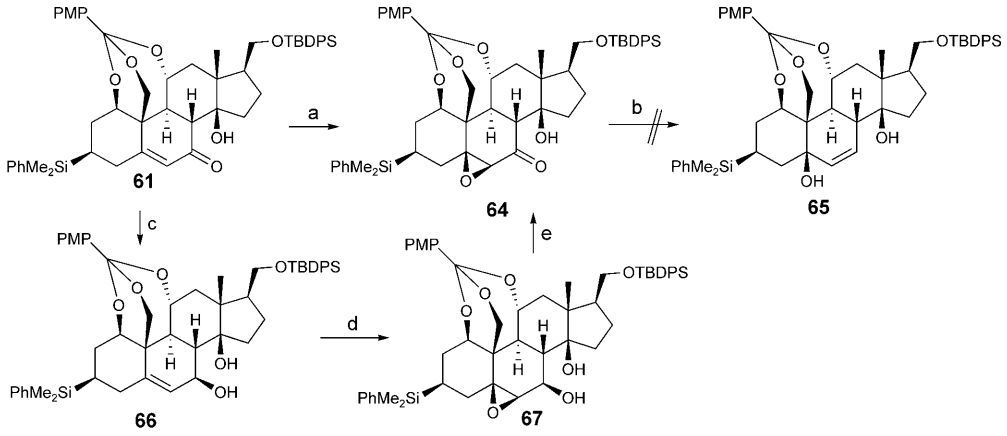
Epoxidation of the enone **61** with alkaline hydrogen peroxide gave β-epoxide **64** in 51% yield with 89% conversion (Scheme 17). However, unrepeatability of this epoxidation on a large scale and failure of the subsequent Wharton reaction[39] (**64** to **65**) led us to the Luche reduction[20] of enone **61** to afford the allylic alcohol **66** exclusively, in 95% yield. Subsequent epoxidation of the allylic alcohol **66** with *m*CPBA almost entirely afforded the 5β,6β-epoxide **67** accompanied by traces of the unwanted 5α,6α-isomer. Oxidation of **67** with Dess–Martin periodinane gave epoxy ketone **64** in low yield. In order to further confirm the stereochemistry, the allylic alcohol **66** was protected as the TBS ether **68** (Scheme 18), in the hope that epoxidation would yield the opposite isomer. However, epoxidation of **68** with *m*CPBA gave epoxide **69**, which was treated with

Scheme 16. Introduction of double bond at Δ^5 through silyl enol ether **59**.

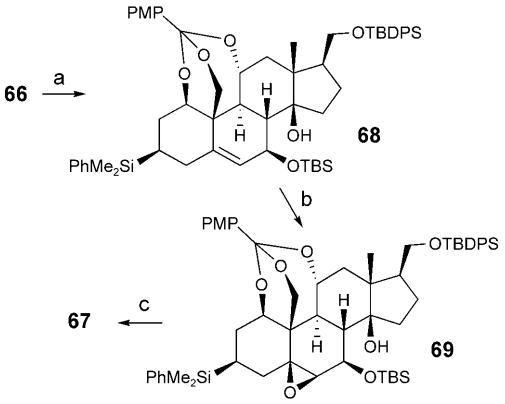
Table 3. Conditions for the oxidation of **59**.

n	Reagents and conditions	**61**:**62**:**63**[a]	Yield
1	PhSeCl, THF, −78°C→RT	–	NR
2	$PhSeOCOCF_3$, CH_2Cl_2, RT→reflux		NR
3	NBS, CH_2Cl_2, RT	–	Undesired
4	$Pd(OAc)_2$, DMSO, RT	100:19:0	<10%
5	$Pd(OAc)_2$ (1.1 equiv), DDQ (3 equiv), MeCN	100:0:24	–
6	$Pd(OAc)_2$ (1.2 equiv), DDQ (3.5 equiv), MeCN, DTBMP[b] (1.5 equiv)	100:0:4	–
7	$Pd(OAc)_2$ (0.8 equiv), DDQ (4 equiv), MeCN, DTBMP[b] (2 equiv)	100:0:0	100%
8	DDQ (4 equiv), MeCN, DTBMP[b] (2 equiv)	100:0:0	100%

[a] The ratio of the products were determined by ^1H NMR; [b] DTBMP = 2,6-di-*tert*-butyl-4-methyl pyridine.



Scheme 17. Selective epoxidation of **61**. a) H_2O_2, NaOH, K_2CO_3, MeOH, 51% in 89% conversion; b) $NH_2NH_2.H_2O$, AcOH, MeOH, CH_2Cl_2 or $NH_2.NH_2.H_2O$, TMSCl, DMF; c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, EtOH, THF, −30°C, 95%; d) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 82%; e) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 12%.



Scheme 18. Selective epoxidation of **66**. a) TBSOTf, Et_3N, CH_2Cl_2, 0 °C, 96 %; b) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 84 %. c) i. TBAF, THF, 0 °C; ii. TBDPSCl, imidazole, DMF, RT, 30 % (two steps).

TBAF to yield the corresponding diol. This compound was then selectively mono-protected as a TBDPS ether to give the epoxy alcohol **67**, as previously obtained. Preferential formation of a β-epoxide is probably because of the presence of the unusual *cis*-CD ring fusion along with the A-ring that blocks the α-face of the boat-like B-ring even if the 7β-hydroxyl group is protected as a TBS ether in compound **68**.

Eventually, the crystalline product **67** provided single crystals that allowed the structure to be confirmed by X-ray diffraction analysis (Figure 2).

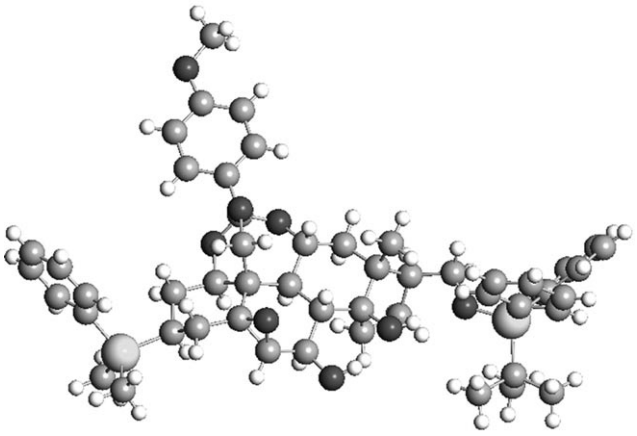
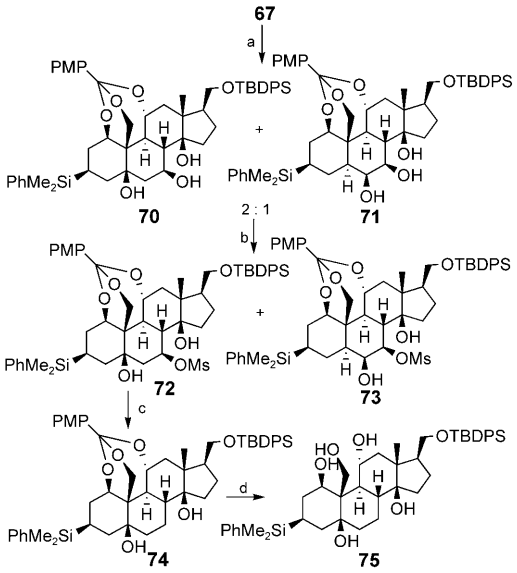


Figure 2. X-ray structure of compound **67.**

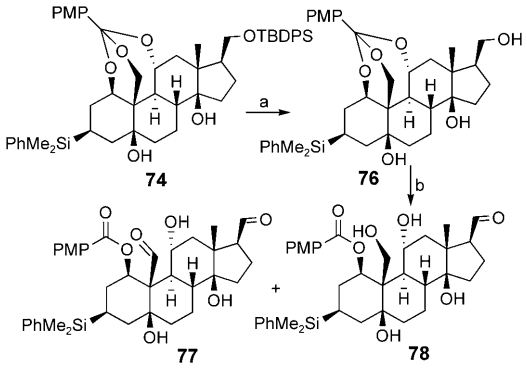
Epoxide **67** was treated with a large excess of lithium borohydride in THF to give an inseparable mixture of the desired product **70** and the regioisomer **71** in the ratio 2:1 (Scheme 19). The mixture, when subjected as such to mesylation, produced chromatographically separable mesylates, with 48 % yield of the desired product **72** over two steps. Hydrogenolysis of the mesylate with $LiBH_4$ in THF afforded diol **74** in 55 % yield.

It is worthwhile to note that all the peaks, except the two methyl groups and the *tert*-butyl group, in the proton NMR



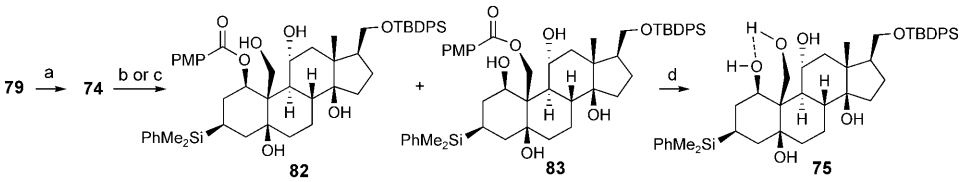
Scheme 19. Reagents and conditions: a) $LiBH_4$, THF, reflux; b) MsCl, pyridine, RT, 48 % for **72**, 21 % for **73** (over two steps); c) $LiBH_4$, THF, reflux, 55 %; d) i. HOAc, THF, H_2O; ii. K_2CO_3, MeOH, THF, 50 %.

of **74** are broadened. These broadened signals indicate that **74** exists in two interconverting conformations. Owing to the A/B-*cis* fusion and the presence of the cyclic orthoester, the A and B rings can take either a chair or a twist-boat conformation, respectively, or vice-versa.[34] Interestingly, compounds **67**, **72**, and **79** do not have this conformational flexibility, probably because the hydrogen bond between 7-OH and 14-OH prevents the conformational flexibility of A and B rings. Compound **74** is not stable in weak acidic conditions, even in chloroform. Treatment of **74** with HOAc afforded a mixture of benzoates, which were hydrolyzed by K_2CO_3 to give pentaol **75**. Compound **74** was treated with TBAF to give triol **76** whose NMR spectrum still displays broadened signals (Scheme 20). When compound **76** was subjected to Dess–Martin periodinane to selectively oxidize the primary alcohol to aldehyde, the orthoester decomposed to give dialdehyde **77** and aldehyde **78**, which yield clear proton NMR spectra and are stable.



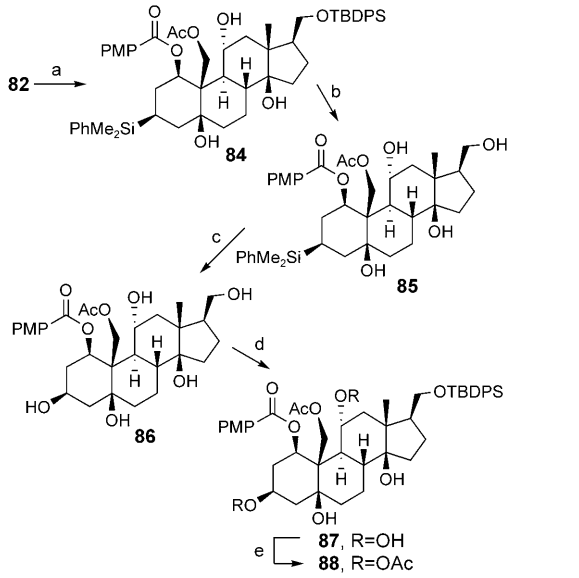
Scheme 20. Reagents and conditions: a) TBAF, THF, 88 %; b) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 37 % for **77**, 15 % for **78**.

Even though this represented an easy approach to the desired pentaol **75**, the low selectivity of epoxide opening prompted us to investigate other methods. Though Red-Al is a good reducing agent for selective opening of acyclic epoxy alcohols,[41] no reaction occurred with epoxy alcohol **67**, which suggests that the bulky hydride reagent does not have access to the reaction center because of the highly hindered α-face of the steroid **67**.

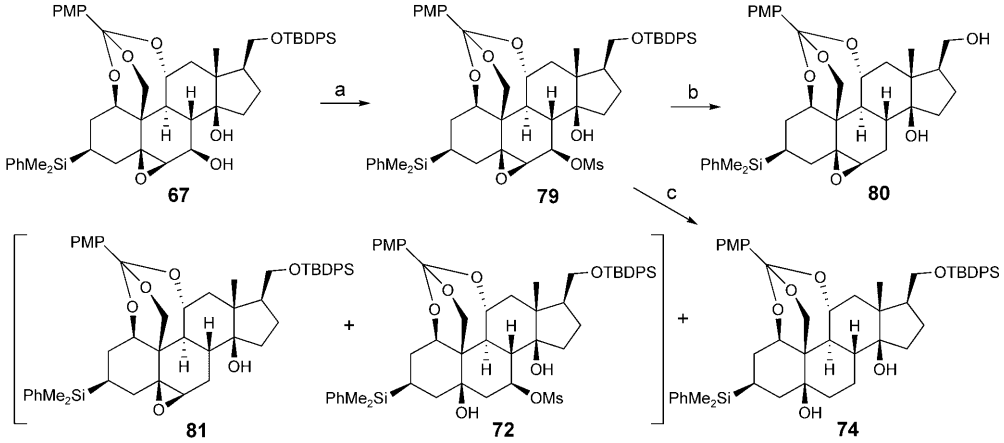


Scheme 22. Reagents and conditions: a) $LiBH_4$ (saturated), THF, overnight; b) $CHCl_3$, RT, overnight, 46% for **82** from **79** (two steps); c) HOAc, THF, H_2O, RT, 82% for a mixture of **82** and **83** from **74**; d) K_2CO_3, MeOH, THF, RT, 62%.

The epoxy alcohol **67** was converted to epoxy mesylate **79**, in the hope for hydrogenolysis of the mesylate and subsequent cleavage of the oxirane ring. Treatment of the epoxy mesylate **79** with lithium aluminium hydride[40] in THF resulted in **80** with the hydrogenolysis of the mesylate as well as the cleavage of the TBDPS group[42] (Scheme 21). However, when mesylate **79** was treated with excess lithium borohydride (about 10 equiv) in THF at RT, only the demesylation product **81** and epoxide-opening product **72** were detected, but **73** was not formed. When this reaction was repeated in reflux THF, **79** gave directly the desired product **74**. When compound **74** was left in $CDCl_3$ at RT overnight, it gave **82** as the main product in 46% yield (Scheme 22). When compound **74** was treated with HOAc, the orthoester was hydrolyzed quickly to afford a mixture of two isomers **82** and **83** (ratio 2:1), which were hydrolyzed with potassium carbonate to give pentaol **75** in 62% yield. Pentaol **75** was treated with acetic anhydride and DMAP to protect the 1,11,19-hydroxyl groups as the literature described for ouabain.[43] However, it turned out that only 19-hydroxyl was protected. An extremely powerful acylation condition (Ac_2O, TMSOTf)[44,45] resulted in a complicated mixture of products. We finally opted for acetylation of tetraol **82** to obtain monoacetate **84**, which was chosen as our key intermediate for unmasking the C3 hydroxyl group (Scheme 23). Removal of the TBDPS group followed by Tamao oxidation[46] of **85** neatly furnished **86** in 93% yield. The primary hydroxyl group of **86** was re-protected as a TBDPS ether (**87**) and the secondary hydroxyl groups as acetates to give the key intermediate **88**.



Scheme 23. Reagents and conditions: a) Ac_2O, DMAP, pyridine, 84%; b) TBAF, THF, 0°C, 99%; c) $Hg(OAc)_2$, AcOH/AcOOH (1:1), RT, 4 h, 93%; d) TBDPSCl, imidazole, CH_2Cl_2, 0°C, 4 h, 75%; e) Ac_2O, py, DMAP, CH_2Cl_2, 40°C, 24 h, 65%.

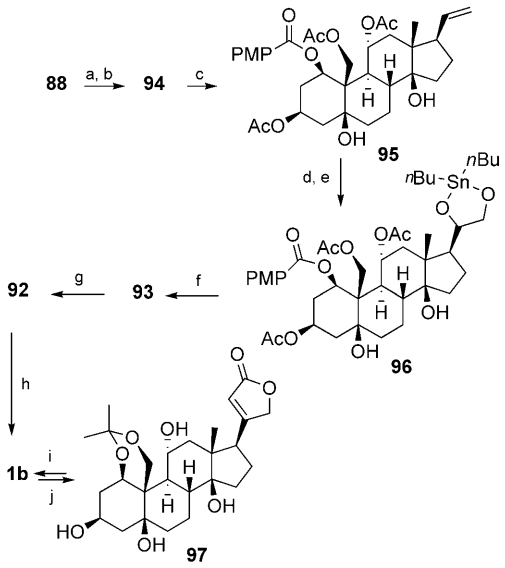


Scheme 21. Reagents and conditions: a) MsCl, pyridine, RT, 94%; b) $LiAlH_4$, THF, reflux, 54%; c) $LiBH_4$ (saturated), THF, RT, 46% for **74**.

Degradation and Completion of the Synthesis of Ouabain

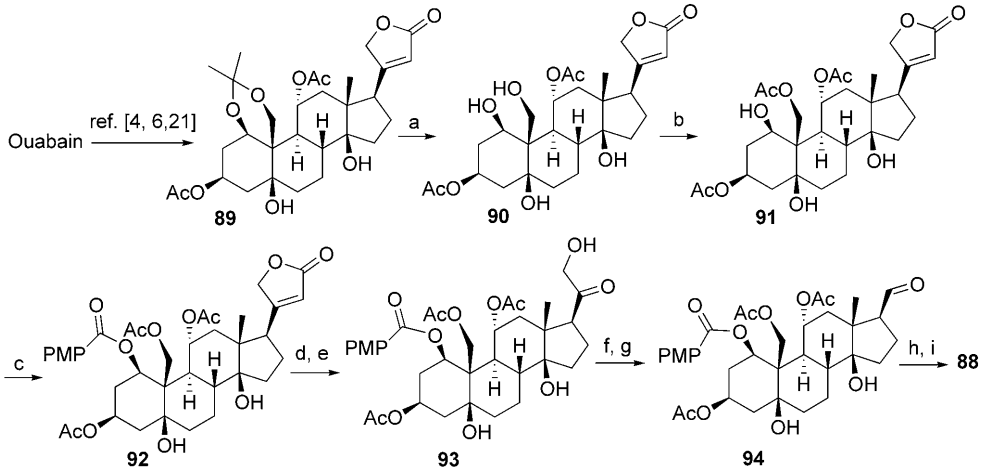
At this stage, with all the required stereochemistry in hand, we wanted to obtain an unambiguous structure confirmation. For that, we opted for the degradation of natural ouabain **1a**[47] to get intermediate **88** and compare it with the synthetic intermediate. Thus, acidic hydrolysis of ouabain[6,7e] in acetone and selective acetylation[48] of secondary hydroxyls resulted in **89**, which on hydrolysis of acetonide group with HCl in MeOH produced tetrol **90** in 52% yield over 3 steps (Scheme 24). The transformation of the primary hydroxyl group of **90** as an acetate and secondary hydroxyl group as *p*-methoxybenzoate gave **92** (via **91**) in 67% overall yield. Ozonolysis of **92** followed by mild hydrolysis ($KHCO_3$ solution) of the resulting formate gave the somewhat less stable hydroxy ketone **93**. Reduction of **93** using $NaBH_4$ in MeOH followed by $NaIO_4$-mediated oxidative cleavage of the resulting 1,2-diol produced aldehyde **94**, which again on reduction, and protection of the resulting primary hydroxyl group as a TBDPS ether cleanly furnished **88** (33% from **92**). This degradation product was completely identical to the synthetic material and was used to complete the total synthesis of ouabagenin and in turn ouabain.

Thus, cleavage of the silyl ether in **88** with TBAF in THF and oxidation of the resulting primary hydroxyl group again gave aldehyde **94** which was transformed into **95** by rhodium-catalyzed methylenation (Scheme 25).[49] After dihydroxylation of the olefin group in **95** with OsO_4 and NMO, **93** was obtained by selective oxidation of the secondary hydroxyl group with NBS via the cyclic tin ether **96**.[50] Construction of the butenolide ring by exposing the hydroxyketone **93** to triphenyl phosphoranylideneketene[51] followed by hydrolysis of acetate groups gave ouabagenin **1b**. Owing to the literature support being limited,[6,52] we decided to obtain a pure sample for the unambiguous comparison. Thus, the hydrolysis of ouabagenin acetonide **97**,[7e,48] obtained from ouabain **1a**, with conc. HCl in MeOH provided an authentic sample of ouabagenin, which, for clarification, was re-protected to ouabagenin acetonide **97** with conc. HCl in acetone. The synthetic ouabagenin was identical with the one obtained from degradation.[53]



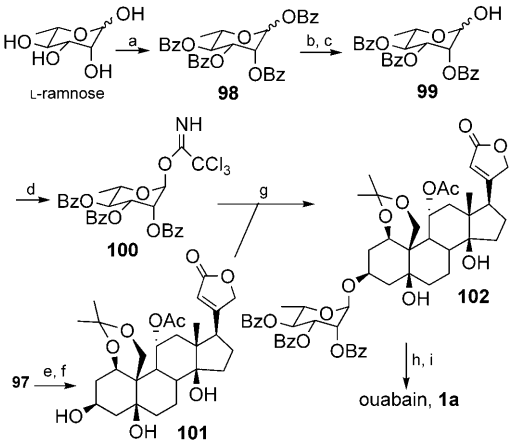
Scheme 25. Completion of the synthesis of ouabagenin **1b**: a) TBAF, THF, 0°C–RT, 2 h, 90%; b) Dess–Martin periodinane, CH_2Cl_2, 0°C, 40 min, 75%; c) $(PPh_3)_3RhCl$, PPh_3, *i*PrOH, $TMSCHN_2$, THF, 16 h, 67%; d) OsO_4, NMO, acetone/H_2O (95:5), 6 h, 82%; e) nBu_2SnO, benzene, reflux, 12 h; f) NBS, $CHCl_3$, 10 min, 73% in two steps; g) Ph_3PCCO, TEA, benzene, RT, 12 h, 68%; h) 0.5 N Na_2CO_3, MeOH, 2 h, RT, 85%.; i) Conc. HCl, MeOH, 50°C, 4 h, 88%; j) Conc. HCl, acetone, RT, 4 h, 80%. NBS = *N*-bromosuccinimide, NMO = 4-methylmorpholine *N*-oxide, TBAF = tetra-*n*-butylammonium fluoride, TEA = triethylamine, TMS = trimethylsilyl.

The remaining part for the completion of the total synthesis of ouabain is described in Scheme 26. To achieve that,



Scheme 24. Degradation of natural ouabain. a) 1 N HCl/MeOH (1:4), 36 h, 90%; b) Ac_2O, py, CH_2Cl_2, 0°C–RT, 6 h, 89%; c) *p*-anisoyl chloride, py, DMAP, CH_2Cl_2, 40°C, 18 h, 76%; d) O_3, CH_2Cl_2, −78°C, 2 h, then Ph_3P, RT, 15 h; e) $KHCO_3$, MeOH:H_2O (1:1), RT, 3 h; f) $NaBH_4$, MeOH, 0°C, 30 min, 51% in 3 steps; g) $NaIO_4$, EtOH:H_2O (95:5), RT, 1 h, 82%; h) $NaBH_4$, MeOH, 0°C, 30 min, 88%; i) TBDPSCl, imidazole, CH_2Cl_2, 0°C–RT, 4 h, 90%. DMAP = *N*,*N*-dimethylaminopyridine, PMP = *p*-methoxyphenyl; py = pyridine, TBDPS = *tert*-butyldiphenyl.

CHEMISTRY
AN ASIAN JOURNAL



Scheme 26. Preparation of glycoside **101** and completion of the total synthesis of ouabain **1a**. Reagents and conditions: a) BzCl, py, DMAP, CH_2Cl_2, RT, 82%; b) AcBr, MeOH, CH_2Cl_2, RT; c) Ag_2CO_3, acetone, H_2O, RT, 58% (2 steps); d) K_2CO_3, CCl_3CN, CH_2Cl_2, RT, 68%; e) Ac_2O, py, DMF, DMAP, 50°C, 78%; f) 0.5 N Na_2CO_3, MeOH, 1 h, RT, 70%; g) TMSOTf, 4 Å MS, CH_2Cl_2, RT, 90%; h) 2 N HCl, MeOH, RT, 2 h, 92%; i) 0.5 N Na_2CO_3, MeOH, 2 h, RT, 88%. Bz = Benzoyl, DMAP = *N,N*-dimethylaminopyridine, MS = molecular sieves, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

we required suitably functionalized coupling partners **100** and **101**. Thus, perbenzoylation of L-rhamnose resulted in **98**, which on anomeric bromination using acetyl bromide and MeOH, followed by hydrolysis with Ag_2CO_3 in aqueous acetone, produced lactol **99**. Treatment of lactol **99** with K_2CO_3 and Cl_3CCN yielded **100** exclusively.[54] The aglycon **101** was easily obtained from **97** by diacetylation[48] followed by selective hydrolysis of C3 acetate group. It was necessary to block the C11−OH group as our initial trials of glycosidation of **101** led to failure of regioselection.

With both building blocks **100** and **101** in hand, the next task was the tethering of the two parts through an acetal bridge. Thus coupling of **100** and **101** was carried out using TMSOTf in CH_2Cl_2 at 0°C to get **102** in 90% yield as the exclusive isomer. Although not unprecedented, the pleasing result with glycosidation was because of anchimeric assistance.[54] For the global deprotection, we treated **102** with mild acid followed by mild basic conditions, as the reverse treatment did not work out satisfactorily, to furnish oubain **1a** in 80% yield in two steps. The synthetic compound was identical with an authentic material.[47,53]

Conclusions

In conclusion, we have successfully completed the first total synthesis of ouabagenin and in turn ouabain through a polyanionic cyclization strategy. The building blocks **20** and **24** were combined and transformed into key tetracyclic intermediate **88** in 19 steps (**25**–**27**→**51**–**54**→**57**→**59**→**61**→**66**-**67**→**79**→**82**→**84**–**88**), which in turn led to ouabagenin (**1b**) in 8 steps (**88**→**94**–**96**→**93**→**92**→**1b**). Finally, ouabagenin (**1b**) was converted into ouabain (**1a**) in 6 steps (**1b**→**97**→**101**–**102**→**1a**). Degradation studies reported here may help the synthetic community in further synthetic studies directed towards this cardioactive steroid.

Experimental Section

Syntheses

26: Cs_2CO_3 (2.09 g, 6.41 mmol) was added to a stirring solution of Nazarov reagent **20** (1.940 g, 3.208 mmol) in CH_2Cl_2 (113 mL). The reaction mixture was stirred at room temperature (RT) for 5 min and then cooled to 0°C. A freshly prepared solution of cyclohexenone **24** (1.66 g, 6.42 mmol) in CH_2Cl_2 (55 mL) was then added to the reaction mixture drop wise in 45 min and stirring continued at 0°C for 10 min. It was then diluted with ethyl acetate and filtered through a pad of silica gel. The solvent was removed in vacuo. Purification of the residue by column chromatography (EtOAc/hexane = 1:4) gave **25** as an oil (2.354 g, 85%).

Tetrakis(triphenylphosphine)palladium (0.121 g, 0.0105 mmol) and morpholine (0.93 mL, 10.66 mmol) was added to a stirring solution of the prepared **25** (3.027 g, 3.507 mmol) in THF (200 mL). The reaction mixture was stirred at RT for 0.5 h. The solvent was removed in vacuo and the remains were taken up with EtOAc, washed with 1 M HCl, saturated $NaHCO_3$, and brine, and dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by column chromatography (EtOAc/hexane = 1:3) afforded the tricycle **26** (1.95 g, 92%) as an oil. $[\alpha]_D^{20} = +91.8$ ($c = 1.27$, $CHCl_3$); IR (NaCl): $\tilde{\nu} = 2957.7$, 1741.0, 1727.8, 1705.6, 1427.1, 1228.7, 1111.8, 823.0, 702.4 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta =$ 9.56 (1H, s, CHO), 7.71–7.65 (4H, m), 7.46–7.33 (11H, m), 5.10 (1H, dd, $J = 6.40$, 8.51 Hz, AcOC*H*), 3.68 (2H, d, $J = 6.50$ Hz, CH_2OTBDPS), 3.13 (1H, dd, $J = 6.04$, 11.94 Hz), 3.05 (1H, m), 2.47–2.40 (2H, m), 2.30–1.92 (9H, m), 1.87 (3H, s, OAc), 1.69–1.38 (5H, m), 1.06 (9H, s, *t*Bu), 0.85 (3H, s, CH_3), 0.29 ppm (6H, s, $SiMe_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta =$ 221.78, 208.31, 207.32, 198.66, 170.29, 135.63, 135.54, 133.73, 129.78, 129.74, 129.62, 128.06, 127.77, 70.03, 64.33, 49.52, 43.31, 42.48, 42.19, 40.85, 40.52, 40.37, 38.64, 36.59, 28.01, 26.93, 26.84, 21.91, 21.87, 21.01, 19.20, 18.90, −5.27, −5.32 ppm; EIMS: *m*/*z* (%): 721 [M^+-C_4H_9], 661, 633, 199, 135. HREIMS: *m*/*z* (%) calcd for $C_{42}H_{49}O_7Si_2$: 721.3017 [*M*-C_4H_9]; found: 721.3024 ± 0.0022.

27: Lithium tris[(3-ethyl-3-pentyl)oxy]aluminohydride (0.5 M in THF, 1.9 mL, 0.95 mmol) was added to a stirring solution of aldehyde **26** (0.3725 g, 0.4781 mmol) in THF (36 mL) at −78°C. The reaction mixture was stirred at −78°C for 24 h. MeOH was added to quench the reaction and the mixture was warmed to 0°C. Et_2O (30 mL) and HOAc solution (5%, 15 mL) were added and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by column chromatography (EtOAc/hexane = 1:2) afforded alcohol **27**(0.3318 g, 89%) as an oil. $[\alpha]_D^{20} = +23.75$ ($c = 1.84$, $CHCl_3$); IR (NaCl): $\tilde{\nu} = 3468.0$ (OH), 2967.9, 1740.0 (C=O), 1709.2 (C=O), 1427.6, 1238.2, 1112.1, 754.9, 702.6 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.70$–7.62 (4H, m), 7.46–7.35 (11H, m), 5.20 (1H, dd, $J =$ 3.90, 10.11 Hz, AcOC*H*), 4.16–4.08 (1H, m, CH_2OH), 3.87–3.77 (1H, m, CH_2OH), 3.71 (2H, d, $J = 6.69$ Hz, CH_2OTBDPS), 3.10 (1H, br s, OH), 2.92 (1H, dd, $J = 5.95$, 10.17 Hz), 2.55–2.29 (5H, m), 2.19–2.01 (6H, m), 1.93 (3H, s, OAc), 1.79–1.71 (2H, m), 1.65–1.55 (1H, m), 1.48–1.26 (3H, m), 1.07 (9H, s, *t*Bu), 0.89 (3H, s, CH_3), 0.30 ppm (6H, s, $SiMe_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 222.03$, 213.04, 209.63, 171.74, 135.45, 133.82, 129.91, 129.85, 129.54, 128.00, 127.89, 127.83, 70.94, 64.68, 62.99, 55.92, 48.88, 44.95, 43.00, 41.02, 39.55, 39.13, 38.91, 37.71, 36.42, 27.10, 26.97, 22.50, 21.92, 21.17, 19.32, 17.02, −4.68, −4.84 ppm; EIMS: *m*/*z* (%): 723 [M^+-C_4H_9], 693 [M^+-C_4H_9-OH], 633, 199, 135, 84; HREIMS: *m*/*z* (%) calcd for $C_{42}H_{51}O_7Si_2$: 723.3173 [*M*-C_4H_9]; found: 723.3163 ± 0.0022.

51: 4-Methoxybenzyl trichloroacetimidate (1.70 g, 6 mmol) and finally lanthanum trifluoromethanesulfonate (88 mg, 0.15 mmol) was added to a solution of alcohol **27** (1.18 g, 1.5 mmol) in toluene (40 mL) at 0°C. The reaction mixture was stirred at 0°C for 10 min and then saturated

$NaHCO_3$ was added to quench the reaction. The mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (EtOAc/hexane = 1:9 to 3:7) to yield 4-methoxybenzyl ether **50** (1.11 g, 76%). $[\alpha]_D^{20} = +16.87$ ($c = 2.68$, $CHCl_3$); IR (NaCl): $\tilde{\nu} = 2956.3$, 1738.2 (C=O), 1711.0 (C=O), 1611.3, 1513.3, 1245.8, 1111.7, 1040.2, 822.9, 702.8 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.68$–7.61 (4H, m), 7.44–7.33 (11H, m), 7.14 (2H, d, $J = 8.67$ Hz, MeO*Ph*-), 6.83 (2H, d, $J = 8.67$ Hz, MeO*Ph*-), 5.27 (1H, dd, $J = 3.70$, 10.03 Hz, AcOC*H*), 4.42 (1H, d, $J = 11.84$ Hz, MeOPhCH_2), 4.22 (1H, d, $J = 11.84$ Hz, MeOPhCH_2), 3.78 (3H, s, CH_3OPh), 3.76–3.59 (4H, m, MPMOCH_2 and CH_2OTBDPS), 2.93 (1H, m), 2.60 (1H, m), 2.50–1.91 (10H, m), 1.88 (3H, s, OAc), 1.71–1.21 (6H, m), 1.05 (9H, s, *t*Bu), 0.84 (3H, s, 13-CH_3), 0.20 ppm (6H, s, $SiMe_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 221.80$, 211.31, 210.53, 170.17, 159.29, 136.38, 135.52, 133.74, 133.31, 133.23, 129.82, 129.66, 129.41, 127.95, 127.84, 127.78, 113.74, 72.89, 70.74, 69.38, 64.57, 55.22, 54.66, 49.26, 43.98, 43.22, 41.99, 40.47, 39.84, 38.84, 37.73, 36.39, 27.36, 26.94, 22.26, 21.62, 21.22, 19.27, 18.26, −4.90, −5.01 ppm; EIMS: *m/z* (%): 882 [M^+-H_2O], 843 [M^+-C_4H_9], 686, 633, 199, 135; HREIMS: *m/z* (%) calcd for $C_{54}H_{66}O_7Si_2$: 882.4347 [*M*-H_2O]; found: 882.4355 ± 0.0026.

52: Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 0.217 mL, 0.110 mmol) was added to a stirring solution of tricycle **51** (0.4900 g, 0.540 mmol) in dry THF (50 mL) at −78 °C. The reaction mixture was then stirred at 63 °C for about 10 min, then cooled to 0 °C, filtered through a pad of silica gel and rinsed with EtOAc. After concentration, purification of the residue was achieved by flash chromatography (EtOAc/hexane = 1:3) to give tetracycle **52** (0.407 g, 83%) as an oil. $[\alpha]_D^{20} = -38.99$ ($c = 4.25$, $CHCl_3$); IR (NaCl): $\tilde{\nu} = 3524.7$ (OH), 2955.2, 1744.0 (C=O), 1698.5 (C=O), 1513.8, 1427.5, 1232.5, 1111.0, 1035.2, 816.1, 702.2 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.66$–7.62 (4H, m), 7.45–7.33 (11H, m), 7.22 (2H, d, $J = 8.68$ Hz, MeO*Ph*-), 6.86 (2H, d, $J = 8.68$ Hz, MeO*Ph*-), 5.01 (1H, m), 4.47 (2H, s, $MeOC_6H_4CH_2$), 3.88–3.73 (3H, m), 3.80 (3H, s, CH_3OPh), 3.68–3.62 (1H, m), 3.53 (1H, s), 2.98–2.89 (3H, m), 2.69–2.54 (2H, m), 2.34–2.29 (1H, m), 2.11–1.92 (5H, m), 1.86 (3H, s, OAc), 1.80–1.55 (4H, m), 1.22–1.15 (2H, m), 1.03 (9H, s, *t*Bu), 0.93 (3H, s, 13-CH_3), 0.27 (3H, s, $SiMe_2$), 0.26 ppm (3H, s, $SiMe_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 213.34$, 210.94, 169.80, 159.22, 137.01, 135.56, 134.13, 133.72, 129.87, 129.48, 129.33, 127.92, 127.54, 113.75, 82.36, 73.57, 69.20, 68.56, 66.65, 55.24, 53.53, 51.84, 51.04, 47.19, 44.73, 43.90, 43.23, 40.62, 37.96, 32.29, 28.77, 26.88, 24.63, 24.23, 20.75, 19.23, 15.32, −3.54, −3.84 ppm; EIMS: *m/z* (%): 882 [M^+-H_2O], 843 (M^+-C_4H_9], 686, 199, 135, 121; HREIMS: *m/z* (%) calcd for $C_{54}H_{66}O_7Si_2$: 882.4347 [*M*-H_2O]; found: 882.4355 ± 0.0026.

53: The acetate **52** (0.4468 g, 0.496 mmol) was dissolved in THF (5.5 mL) and MeOH (5.5 mL). Powder K_2CO_3 (0.0982 g, 0.712 mmol) was added and the reaction mixture was stirred at RT overnight. EtOAc was added to dilute the reaction. It was filtered through a pad of silica gel. Purification of the residue by flash chromatography (EtOAc/hexane = 1:2) gave the corresponding alcohol **53** (0.4165 g, 98%) as an oil. $[\alpha]_D^{20} = +58.66$ ($c = 2.61$, $CHCl_3$); IR (NaCl): $\tilde{\nu} = 3500.4$ (OH), 2954.6, 1694.6 (C=O), 1611.8, 1513.6, 1427.4, 1249.7, 1111.2, 1081.8, 820.5, 702.0 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.69$–7.66 (4H, m), 7.44–7.35 (11H, m), 7.22 (2H, d, $J = 8.60$ Hz, MeO*Ph*-), 6.89 (2H, d, $J = 8.60$ Hz, MeO*Ph*-), 4.54 (1H, d, $J = 11.64$ Hz, $MeOC_6H_4CH_aH_b$), 4.36 (1H, d, $J = 11.64$ Hz, $MeOC_6H_4CH_aH_b$), 3.95 (1H, s), 3.92–3.75 (4H, m), 3.82 (3H, s, CH_3OPh), 3.71–3.65 (1H, m), 3.05 (1H, d, $J = 6.85$ Hz, 8-H), 2.76–2.81 (1H, m), 2.67–2.51 (2H, m), 2.41–2.19 (3H, m), 2.02–1.66 (8H, m), 1.40–1.28 (3H, m), 1.06 (9H, s, *t*Bu), 0.91 (3H, s, 13-CH_3), 0.26 ppm (6H, s, $SiMe_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 216.65$, 215.98, 159.54, 135.87, 135.72, 135.62, 135.56, 134.35, 134.24, 133.73, 129.84, 129.76, 129.57, 129.43, 128.96, 128.03, 127.53, 113.92, 83.70, 73.11, 68.11, 66.95, 66.28, 56.08, 55.26, 51.38, 50.71, 48.06, 46.98, 43.37, 41.16, 40.41, 37.00, 32.62, 27.89, 26.93, 24.38, 22.59, 19.26, 15.44, −5.23, −5.58 ppm; EIMS: *m/z* (%) 840 [M^+-H_2O], 822 [M^+-2H_2O], 801 [M^+-C_4H_9], 783, 199, 135, 121; HREIMS: *m/z* (%) calcd for $C_{52}H_{64}O_6Si_2$: 840.4241 [*M*-H_2O]; found: 840.4268 ± 0.0025.

54: $NaBH_4$ (1.67 mg, 0.0441 mmol) in EtOH (0.8 mL) was added slowly to a solution of ketone **53** (63.3 mg, 0.0737 mmol) in EtOH (2 mL) at −78 °C. After the mixture was stirred at −78 °C for 2 h, it was poured into saturated NH_4Cl solution (8 mL), extracted with EtOAc, washed with brine, and dried over Na_2SO_4. Purification of the residue by flash chromatography (EtOAc/hexane = 1:1) gave triol **54** (61.6 mg, 97%) as an oil. $[\alpha]_D^{20} = +10.19$ ($c = 2.11$, $CHCl_3$); IR (NaCl): $\tilde{\nu} = 3491.9$ (OH), 3189.2 (OH), 2930.3, 1697.6 (C=O), 1611.3, 1512.5, 1427.3, 1250.0, 1111.3, 1082.3, 822.4, 701.4 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.69$–7.66 (4H, m), 7.45–7.32 (11H, m), 7.20 (2H, d, $J = 8.64$ Hz, MeO*Ph*-), 6.86 (2H, d, $J = 8.64$ Hz, MeO*Ph*-), 4.52 (1H, d, $J = 11.63$ Hz, $MeOC_6H_4CH_aH_b$), 4.29 (1H, d, $J = 11.63$ Hz, $MeOC_6H_4CH_aH_b$), 4.18–4.10 (1H, m), 4.09 (1H, s), 3.80 (3H, s, CH_3OPh), 3.86–3.60 (4H, m), 3.55 (1H, d, $J = 10.03$ Hz), 2.86 (1H, d, $J = 13.24$ Hz, 8-H), 2.67–2.48 (2H, m), 1.94–1.56 (10H, m), 1.37–1.14 (5H, m), 1.06 (9H, s, *t*Bu), 0.93 (3H, s, 13-CH_3), 0.93–0.85 (1H, m), 0.22 (3H, s, $SiMe_2$), 0.21 ppm (3H, s, $SiMe_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 218.31$, 159.30, 137.13, 135.72, 135.62, 135.52, 134.33, 134.19, 133.75, 129.36, 129.78, 129.70, 129.44, 129.15, 127.83, 127.54, 113.75, 83.57, 75.39, 72.93, 66.93, 66.29, 65.79, 55.24, 51.31, 51.12, 49.28, 47.92, 46.68, 44.68, 42.70, 32.42, 32.18, 31.05, 27.49, 26.95, 24.34, 19.27, 17.36, 15.40, −5.30, −5.62 ppm; EIMS: *m/z* (%): 842 [M^+-H_2O], 824 [M^+-2H_2O], 803 [M^+-C_4H_9], 785, 477, 199, 121; HREIMS: *m/z* (%) calcd for $C_{52}H_{66}O_6Si_2$: 842.4398 [*M*-H_2O]; found: 842.4393 ± 0.0025.

57: PMB ether **54** (0.3667 g, 0.426 mmol) was dissolved in CH_2Cl_2 (40 mL) at RT and then powder 4 Å molecular sieves were added. After stirring at RT for 1 h, DDQ (0.3866 g, 1.703 mmol) was added. The mixture was stirred at RT for 39 h, and filtered through a pad of silica gel. The filtrate was washed with an aqueous solution of $NaHCO_3$, then dried with $MgSO_4$ and concentrated. Further purification of the residue by flash chromatography (EtOAc/hexane = 1:4) gave *ortho*-ester **57** (0.3073 g, 84%) and a mixture of acetals **55** and **56** (0.0406 g, 11%), which can be converted to orthoester **57** with the above conditions. $[\alpha]_D^{20} = +44.07$ ($c = 1.97$, $CHCl_3$); IR (NaCl): $\tilde{\nu} = 3493.8$ (OH), 2932.4, 1699.4 (C=O), 1612.0, 1514.9, 1427.5, 1298.0, 1249.1, 1112.1, 832.1, 701.2 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.72$–7.67 (4H, m), 7.56 (2H, d, $J = 8.92$ Hz, MeO*Ph*-), 7.50–7.36 (11H, m), , 6.88 (2H, d, $J = 8.92$ Hz, MeO*Ph*-), 4.30–4.19 (2H, m), 4.15–4.06 (2H, m), 4.01 (1H, s, OH), 3.89–3.84 (1H, m), 3.81 (3H, s, CH_3OPh), 3.74–3.69 (1H, m), 2.65 (1H, dd, $J = 14.50$, 16.06 Hz, 9-H), 2.49 (1H, d, $J = 13.75$ Hz, H-8), 2.12–1.77 (9H, m), 1.71–1.48 (4H, m), 1.39–1.34 (1H, m), 1.08 (3H, s, 13-CH_3), 1.07 (9H, s, *t*Bu), 1.00–0.86 (1H, m), 0.32 ppm (6H, s, $SiMe_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 216.25$, 159.86, 136.64, 135.62, 134.23, 134.15, 133.78, 133.49, 129.48, 129.38, 127.98, 127.89, 127.58, 127.49, 127.04, 127.00, 126.96, 113.21, 110.27, 83.51, 79.16, 68.02, 66.78, 65.34, 55.32, 51.62, 50.25, 48.64, 47.15, 43.90, 43.39, 36.58, 33.73, 33.11, 30.84, 28.64, 26.93, 24.44, 19.27, 17.38, 15.98, −5.09, −5.44 ppm; EIMS: *m/z* (%): 838 [M^+-H_2O], 799 [M^+-C_4H_9], 781, 199, 135; HREIMS: *m/z* (%) calcd for $C_{52}H_{62}O_6Si_2$: 838.4085 [*M*-H_2O]; found: 838.4076 ± 0.0025.

59: *tert*-Butyldimethylsilyl trifluoromethanesulfonate (0.81 mL, 3.54 mmol) was added dropwise to a mixture of Et_3N (1.23 mL, 8.82 mmol) and CH_2Cl_2 (0.5 mL) at 0 °C. Then a solution of ketone **57** (0.2014 g, 0.235 mmol) in CH_2Cl_2 (1.5 mL) was added drop wise. It was warmed up to RT and stirred for 4.5 h. *i*PrOH (0.36 mL, 4.64 mmol) was added to quench the reaction at 0 °C. The mixture was filtered through a pad of silica gel. Further purification of the residue by flash chromatography (EtOAc/hexane = 1:6) gave the TBS enol ether **59** (0.1545 g, 90%). Some starting material (0.0504 g, conversion 75%) was also recovered. $[\alpha]_D^{20} = +34.9$ ($c = 1.19$, $CHCl_3$); IR (NaCl): $\tilde{\nu} = 3521.4$ (OH), 2954.2, 1673.0, 1613.7, 1515.6, 1249.1, 1111.9, 831.8, 701.0 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.70$–7.65 (4H, m), 7.54–7.49 (4H, m), 7.44–7.33 (9H, m), 6.85 (2H, d, $J = 8.88$ Hz, MeO*Ph*-), 4.42 (1H, dd, $J = 1.97$, 4.86 Hz, 6-H), 4.26 (1H, dt, $J = 2.75$, 10.88 Hz, 11-H), 4.05 (1H, dd, $J = 4.04$, 11.96 Hz, 1-H), 3.98 (1H, s, OH), 3.87–3.80 (2H, m), 3.79 (3H, s, CH_3OPh), 3.78–3.67 (2H, m), 2.40 (1H, d, $J = 10.83$, 8-H), 1.98–1.55 (10H, m), 1.45–1.19 (4H, m), 1.08 (3H, s, 13-CH_3), 1.05 (9H, s, *t*Bu), 0.93 (9H, s, *t*Bu), 0.32 (3H, s, *t*BuSiMe_2), 0.31 (3H, s, *t*BuSiMe_2), 0.19 (3H, s, PhSiMe_2), 0.18 ppm (3H, s, PhSiMe_2); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 159.76$, 149.09, 137.24, 135.62, 134.29, 134.26, 133.79, 133.34, 129.41, 129.38, 129.27, 127.82, 127.50, 126.73, 126.69, 113.22, 111.43, 107.08, 84.81, 78.65, 70.63, 65.88, 65.06, 55.31, 52.86, 49.01, 48.59, 47.17, 43.59, 36.82, 34.37, 33.32, 28.65, 26.93, 26.89, 26.03, 25.50, 25.02, 19.25, 18.21, 18.07, 16.43,

−4.14, −4.25, −4.98, −5.43 ppm; EIMS: *m/z* (%): 913 [M^+-C_4H_9], 761, 627, 199, 135; HREIMS: *m/z* (%) calcd for $C_{54}H_{69}O_7Si_3$: 913.4351 [M-C_4H_9]; found: 913.4344 ± 0.0027.

61: A suspension of TBS enol ether **59** (0.1479 g, 0.152 mmol), DDQ (0.1382 g, 0.609 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (62.5 mg, 0.304 mmol) in MeCN (20 mL) was stirred at RT overnight. It was then diluted with CH_2Cl_2 (10 mL) and filtered through a pad of silica gel, and washed with hexane-EtOAc (2:1). The filtrate was then washed with an aqueous solution of $NaHCO_3$, dried with $MgSO_4$, filtrated and concentrated. Further purification of the residue by flash chromatography (EtOAc/hexane = 1:3) gave the enone **61** (0.1301 g, 100%) as a solid. $[\alpha]_D^{20}$ = +15.15 (c = 1.65, $CHCl_3$); IR (NaCl): $\tilde{\nu}$ = 3480.7 (OH), 2934.8, 1654.1 (C=O), 1613.1, 1588.2, 1248.8, 1112.1, 831.6, 701.0 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.71–7.67 (4H, m), 7.55 (2H, d, J = 8.88 Hz, *Ph*OMe), 7.51–7.36 (11H, m), 6.89 (2H, d, J = 8.88 Hz, MeO*Ph*-), 5.91 (1H, s, 6-H), 4.34 (1H, s, OH), 4.35–4.22 (3H, m), 4.05 (1H, dd, J = 5.95, 9.42 Hz, 1-H), 3.88 (1H, dd, J = 5.92, 9.85 Hz, 20-H_a), 3.82 (3H, s, CH_3OPh), 3.73 (1H, dd, J = 7.48, 9.80 Hz, 20-H_b), 2.65 (1H, d, J = 13.39 Hz, 8-H), 2.30–1.76 (12H, m), 1.62–1.54 (1H, m), 1.13 (3H, s, 13-CH_3), 1.08 (9H, s, *t*Bu), 0.36 (3H, s, PhSiMe_2), 0.35 ppm (3H, s, PhSiMe_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 200.55, 161.71, 159.99, 135.95, 135.63, 135.60, 134.29, 134.21, 133.82, 133.12, 129.59, 129.47, 128.62, 128.08, 127.57, 126.92, 113.28, 110.16, 83.59, 81.13, 68.78, 66.74, 63.50, 55.34, 53.37, 51.79, 47.73, 47.25, 44.47, 42.29, 35.42, 33.25, 32.18, 26.94, 24.99, 22.70, 19.28, 16.50, −5.20, −5.47 ppm; EIMS: *m/z* (%): 854 [M^+], 836 [M^+-H_2O], 797 [M^+-C_4H_9], 779, 199, 135; HREIMS: *m/z* (%) calcd for $C_{52}H_{60}O_6Si_2$: 836.3928 [M^+-H_2O]; found: 836.3934 ± 0.0025.

66: The enone **61** (0.2165 g, 0.253 mmol) was dissolved in THF (7.2 mL) and EtOH (3.6 mL). This solution was cooled to −40 °C and a solution of $NaBH_4$ (0.0105 g, 0.277 mmol) in EtOH (1.7 mL) was added. After stirring at −30 °C for 2 h, the reaction was quenched by addition of saturated NH_4Cl. The mixture was extracted with EtOAc, washed with brine, and dried over Na_2SO_4. Purification of the residue by flash chromatography (EtOAc/hexane = 1:3) gave the allylic alcohol **66** (0.2061 g, 95%) as a solid. $[\alpha]_D^{20}$ = +21.59 (c = 2.64, $CHCl_3$); IR (NaCl): $\tilde{\nu}$ = 3332.1 (OH), 2934.0, 1717.8, 1612.2, 1588.4, 1427.6, 1293.7, 1248.5, 1113.3, 1028.2, 832.3, 701.0 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.69–7.66 (4H, m), 7.55–7.36 (13H, m), 6.84 (2H, d, J = 8.91 Hz, MeO*Ph*-), 5.65 (1H, s, 6-H), 5.38–4.34 (2H, m), 4.24 (1H, dt, J = 3.75, 9.96 Hz, 11-H), 4.14 (1H, dd, J = 1.56, 10.40 Hz), 3.78 (3H, s, CH_3OPh), 3.77–3.73 (2H, m), 3.43 (1H, dd, J = 3.00, 10.80 Hz, 20-H_a), 2.27–1.73 (12H, m), 1.61–1.53 (1H, m), 1.24 (3H, s, 13-CH_3), 1.09 (9H, s, *t*Bu), 0.85–0.98 (1H, m), 0.32 ppm (6H, s, PhSiMe_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.75, 137.01, 135.87, 135.71, 135.28, 133.85, 131.85, 131.70, 130.44, 130.16, 129.22, 127.89, 126.99, 113.13, 109.46, 85.23, 81.09, 68.76, 68.19, 65.27, 64.38, 55.29, 51.03, 50.42, 48.33, 44.04, 42.48, 41.07, 33.80, 33.45, 32.34, 26.77, 23.70, 21.39, 19.16, 16.47, −5.16, −5.19 ppm; EIMS: *m/z* (%): 856 [M^+], 838 [M^+-H_2O], 820, 199, 136; HREIMS: *m/z* (%) calcd for $C_{52}H_{64}O_7Si_2$: 856.4190 [M^+]; found: 856.4205 ± 0.0026.

67: To a solution of allylic alcohol **66** (20.1 mg, 0.0234 mmol) in CH_2Cl_2 (0.5 mL) $NaHCO_3$ (14.5 mg, 0.173 mmol) was added. The mixture was cooled to 13 °C, and *m*-chloroperbenzoic acid (80%, 10.1 mg, 0.0468 mmol) was added. The mixture was stirred at this temperature for 24 h and then quenched with an aqueous solution of $NaHCO_3$. The mixture was extracted with CH_2Cl_2, washed with brine, dried with $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (hexane/EtOAc/CH_2Cl_2 = 9:0.5:0.5) gave the desired epoxide **67** (85%). $[\alpha]_D^{20}$ = +17.14 (c = 1.3, $CHCl_3$); IR (NaCl): 3330.3 (OH), 2935.1, 1612.3, 1588.3, 1514.7, 1427.7, 1249.7, 1113.9, 1027.6, 833.0, 758.2, 701.5 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.67–7.64 (4H, m), 7.52–7.34 (13H, m), 6.83 (2H, d, J = 8.91 Hz, MeO*Ph*-), 5.98 (1H, s, OH), 5.86 (1H, s, OH), 4.36–4.28 (2H, m, 19-H), 4.21–4.12 (2H, m), 3.98 (1H, dd, J = 5.69, 10.94 Hz, 1-H), 3.78 (3H, s, CH_3OPh), 3.71 (1H, d, J = 10.13 Hz, 20-H_a), 3.40 (1H, dd, J = 2.99, 10.80 Hz, 20-H_b), 3.10 (1H, s, 6-H), 2.20–1.21 (13H, m), 1.18 (3H, s, 13-CH_3), 1.06 (9H, s, *t*Bu), 1.01–0.85 (1H, m), 0.31 (3H, s, PhSiMe_2), 0.30 ppm (3H, s, PhSiMe_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.79, 136.35, 135.84, 135.70, 133.82, 133.49, 131.74, 131.65, 130.17, 129.38, 127.95, 127.89, 126.89, 113.16, 109.59, 84.32, 81.73, 70.30, 68.00, 66.03, 64.26, 63.39, 62.96, 55.29, 52.90, 50.81, 48.30, 44.05, 38.43, 38.07, 34.18, 33.13, 31.74, 26.75, 21.25, 19.14, 18.32, 16.30, −5.34, −5.42 ppm; EIMS: *m/z* (%): 872 [M^+], 815 [M^+-C_4H_9], 663, 199, 152, 135; HREIMS: *m/z* (%) calcd for $C_{52}H_{64}O_8Si_2$: 872.4139 [M^+]; found: 872.4148 ± 0.0026.

79: A solution of MsCl (10.7 mL, 0.138 mmol) in pyridine (0.2 mL) was added to a solution of the alcohol **67** (60.3 mg, 0.069 mmol) in pyridine (2 mL) at 0 °C. The reaction mixture was stirred at RT overnight. Saturated $NaHCO_3$ solution was added and the mixture was extracted with EtOAc, washed with water and brine, and then dried with Na_2SO_4. Purification of the residue by flash chromatography (EtOAc/hexane/CH_2Cl_2 = 1:6:7) gave the mesylate **79** (61.7 mg, 94%). $[\alpha]_D^{20}$ = +37.70 (c = 0.87, $CHCl_3$); IR (NaCl): $\tilde{\nu}$ = 3532.4, 3400.2 (OH), 2936.3, 1612.7, 1515.4, 1427.7, 1318.9, 1250.2, 1169.7, 1112.8, 934.8, 831.9, 701.5 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.67–7.63 (4H, m), 7.49–7.35 (13H, m), 6.83 (2H, d, J = 8.87 Hz, MeO*Ph*-), 5.30 (1H, dd, J = 0.98, 9.97 Hz, 7-H), 4.30 (1H, s, OH), 4.26 (2H, m, 19-H), 4.18 (1H, dt, J = 3.68, 11.31 Hz, 11-H), 3.98 (1H, dd, J = 5.94, 10.86 Hz, 1-H), 3.78 (3H, s, CH_3OPh), 3.72 (1H, dd, J = 2.23, 10.70 Hz, 20-H_a), 3.49 (1H, dd, J = 3.59, 10.70 Hz, 20-H_b), 3.29 (1H, d, J = 0.98 Hz, 6-H), 3.05 (3H, s, OMs), 2.42 (1H, dd, J = 10.01, 12.49 Hz, 8-H), 2.19–1.17 (12H, m), 1.18 (3H, s, 13-CH_3), 1.06 (9H, s, *t*Bu), 1.01–0.85 (1H, m), 0.30 (3H, s, PhSiMe_2), 0.29 ppm (3H, s, PhSiMe_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.86, 135.97, 135.75, 135.70, 135.66, 133.83, 133.09, 132.25, 130.01, 129.46, 129.12, 128.00, 127.83, 126.82, 113.19, 109.72, 82.57, 81.16, 78.21, 67.92, 64.74, 64.52, 64.36, 62.97, 55.29, 53.91, 51.15, 48.50, 44.54, 39.47, 38.88, 38.23, 34.10, 32.90, 31.89, 26.90, 21.73, 19.28, 17.89, 16.58, −5.28, −5.53 ppm; EIMS: *m/z* (%): 893 [M^+-C_4H_9, 0.5], 854 [M^+-CH_3SO_3H], 836, 797, 215, 199, 135; HREIMS: *m/z* (%) calcd for $C_{52}H_{62}O_7Si_2$: 854.4034 [M^+-MsOH]; found: 854.4039 ± 0.0025.

82: To the epoxide **79** (22.5 mg, 0.023 mmol) in DME (0.8 mL) $LiBH_4$ (12.8 mg, 0.587 mmol) was added at 0 °C and the mixture was stirred at RT overnight for 24 h and at reflux for 8 h. Then the reaction mixture was diluted with Et_2O and poured into saturated NH_4Cl solution at 0 °C. The mixture was stirred at RT for 2 h, extracted with EtOAc, dried with Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane/EtOAc = 2.5:1–1.1) gave **82** (9.6 mg, 58%); IR (NaCl): $\tilde{\nu}$ = 3414, 2931, 1705, 1606, 1510, 1255, 1166, 1111, 756, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.68–7.59 (6H, m), 7.46–7.35 (8H, m), 7.11–7.02 (3H, m), 6.86 (2H, d, J = 8.91 Hz, PhOMe), 4.83 (1H, br s, 1-H), 4.52 (1H, s, OH), 4.38 (1H, d, J = 12.2 Hz, 19-Ha), 3.86 (3H, s, $PhOCH_3$), 3.90–3.83 (1H, m), 3.69 (1H, d, J = 10.66 Hz, 20 Hz), 3.57 (1H, t, J = 11.20 Hz, 19-Hb), 3.40 (1H, dd, J = 3.15, 10.74 Hz, 20-Hb), 3.03–2.97 (1H, m), 2.55 (1H, dd, J = 9.49, 17.14 Hz), 2.23–1.21 (18H, m), 1.09 (3H, s, 13-CH_3), 1.08 (9H, s, *t*Bu), 0.90–0.82 (1H, m), 0.21 (3H, s, PhSiMe_2), 0.20 ppm (3H, s, PhSiMe_2); EIMS: *m/z* (%): 783 [M^+-C_4H_9-2H_2O], 649, 631, 199, 135; HREIMS: *m/z* (%) calcd for $C_{48}H_{55}O_6Si_2$: 783.3537 [M^+-C_4H_9-2H_2O]; found: 783.3551 ± 0.0023.

84: A mixture of alcohol **82** (60 mg, 0.068 mmol), Ac_2O (35 mg, 0.34 mmol) and DMAP in pyridine (2 mL) was stirred at RT for 24 h and water was added before extracting with CH_2Cl_2. The combined organic layers were washed with $CuSO_4$ solution and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography to get the corresponding primary acetate **84** (40 mg, 65%); IR (NaCl): $\tilde{\nu}$ = 3414, 2932, 1739, 1705, 1606, 1427, 1254, 1111, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.78 (2H, d, J = 8.93 Hz, *Ph*OMe), 7.68–7.64 (4H, m), 7.49–7.34 (8H, m), 7.12–7.08 (3H, m), 6.85 (2H, d, J = 8.93 Hz, *Ph*OMe), 4.60 (1H, d, J = 12.25 Hz, 19-H_a), 4.47 (1H, s, OH), 4.43 (1H, br s, 1-H), 4.34 (1H, d, J = 12.25 Hz, 19-H_b), 4.08–4.00 (1H, m), 3.86 (3H, s, PhOCH_3), 3.81 (1H, s, OH), 3.69 (1H, d, J = 10.66 Hz, 20-Ha), 3.41 (1H, dd, J = 3.21 10.73 Hz, 20-H_b), 2.98–2.92 (1H, m), 2.63 (1H, dd, J = 9.42, 17.09 Hz), 2.09 (3H, s, OAc), 2.13–1.25 (16H, m), 1.08 (9H, s, *t*Bu), 1.05 (3H, s, 13-CH_3), 0.95–0.83 (1H, m), 0.19 ppm (6H, s, PhSiMe_2).

85: TBAF (1 M solution, 0.3 mL, 0.3 mmol) was added to the above TBDPS ether **84** (200 mg, 0.21 mmol) in THF (1 mL) at 0 °C and stirred at the same temperature for 1 h. The reaction mixture was then quenched with saturated ammonium chloride solution and extracted with EtOAC

(3×3 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (80% EtOAc/hexane) to afford **85** (130 mg, 88%). $[\alpha]_D^{20}=-16.76$ ($c=1.3$, $CHCl_3$); IR (NaCl): $\tilde{\nu}=3390.2$, 3012.2, 2963.4, 2939.1, 1737.8, 1701.2, 1603.7, 1256.1, 1170.7, 1115.9, 1036.6, 841.4 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta=7.77$ (d, 2H, $J=8.78$ Hz), 7.42–7.35 (m, 2H), 7.16–7.07 (m, 3H), 6.86 (d, 2H, $J=8.78$ Hz), 4.60 (d, 1H, $J=12.35$ Hz), 4.45 (t, 1H, $J=2.20$ Hz), 4.33 (d, 1H, $J=12.35$ Hz), 4.02 (dt, 1H, $J=11.25$, 4.67 Hz), 3.87 (s, 3H), 3.80 (dd, 1H, $J=10.70$, 1.92 Hz), 3.54 (dd, 1H, $J=10.70$, 3.57 Hz), 3.02–2.91 (m, 1H), 2.63 (dd, 1H, $J=17.02$, 9.61 Hz), 2.09 (s, 3H), 2.07–1.77 (m, 12H), 1.71–1.53 (m, 3H), 1.44–1.21 (m, 2H), 1.09 (s, 3H), 0.21 ppm (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=171.04$, 164.92, 163.12, 136.62, 133.86, 131.34, 128.87, 127.58, 124.03, 113.34, 84.97, 84.48, 78.07, 72.94, 64.83, 62.06, 55.43, 51.32, 51.03, 50.59, 46.86, 44.56, 35.46, 32.57, 32.49, 27.15, 26.25, 25.21, 21.62, 21.25, 16.13, 13.81, 10.65 ppm; EIMS: m/z (%): 663 [M-OH], 135; HREIMS: m/z (%) calcd for $C_{38}H_{51}O_8S_i$: 663.3353 [M-OH]; found: 663.3344±0.0020.

86: To a stirred mixture of compound **85** (8 mg, 0.012 mmol) AcOH (0.3 mL) and AcOOH (35% in AcOH, 0.3 mL) $Hg(OAc)_2$ (18 mg, 0.06 mmol) was added and the reaction mixture was stirred for 4 h at room temperature before being quenched with 5% $Na_2S_2O_3$ solution at 0°C. The mixture was extracted with CH_2Cl_2 (3×2 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (EtOAc) to give **86** (6 mg, 93%) as a white solid. $[\alpha]_D^{20}=+2.9$ ($c=0.5$, $CHCl_3$); IR (NaCl): $\tilde{\nu}=3393$, 3004, 2935, 1737, 1700, 1604, 1508, 1458, 1097, 1033 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta=7.95$ (d, 2H, $J=8.78$ Hz), 6.90 (d, 2H, $J=8.78$ Hz), 4.61 (s, 2H), 4.54 (t, 1H, $J=6.86$ Hz), 4.25–4.15 (m, 1H), 4.08 (dt, 1H, $J=11.53$, 4.69 Hz), 3.86 (s, 3H), 3.82 (dd, 1H, $J=11.53$, 2.20 Hz), 3.55 (dd, 1H, $J=11.53$, 3.02 Hz), 3.10–2.96 (m, 2H), 2.40–2.25 (m, 1H), 2.19–1.86 (m, 8H), 2.14 (s, 3H), 1.79–1.48 (m, 4H), 1.79–1.48 (m, 2H), 1.10 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=170.79$, 165.38, 163.37, 131.56, 123.92, 113.62, 86.33, 84.26, 77.16, 73.73, 65.50, 63.62, 62.19, 55.45, 50.96, 50.60, 48.96, 47.43, 45.85, 37.77, 36.37, 33.31, 32.50, 29.69, 24.93, 21.73, 21.31, 16.22 ppm; EIMS: m/z (%): 544 [M-H_2O], 81; HREIMS: m/z (%) calcd for $C_{30}H_{40}O_9$: 544.2672 [M-H_2O]; found: 544.2679±0.0016.

88: TBDPSCl (4.5 mg, 0.015) was added to a mixture of the alcohol **86** (6 mg, 0.01 mmol) and imidazole (3.6 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) at 0°C and stirred at the same temperature for 4 h. The reaction mixture was quenched with saturated ammonium chloride solution at 0°C and extracted with EtOAc (3×2 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to silica gel column chromatography (30% EtOAc/hexane) to afford the primary TBDPS ether **87** (6 mg, 75%). $[\alpha]_D^{20}=-5.6$ ($c=0.6$, $CHCl_3$); IR (NaCl): $\tilde{\nu}=3390.2$, 2963.4, 2932.9, 2853.7, 1737.8, 1609.8, 1286.6, 1256.1, 1207.3, 1097.6, 1036.6 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta=7.94$ (d, 2H, $J=9.06$ Hz), 7.63–7.54 (m, 4H), 7.44–7.26 (m, 6H), 6.86 (d, 2H, $J=9.06$ Hz), 4.57 (s, 2H), 4.42 (t, 1H, $J=5.49$ Hz), 4.16–4.04 (m, 1H), 3.92 (dt, 1H, $J=4.67$, 11.80 Hz), 3.74 (dd, 1H, $J=1.37$, 11.53 Hz), 3.47 (dd, 1H, $J=3.29$, 11.53 Hz), 3.09 (dd, 1H, $J=5.76$, 17.29 Hz), 3.01–2.90 (m, 1H), 2.11 (s, 3H), 2.01–1.67 (m, 6H), 1.65–1.38 (m, 4H), 1.36–1.08 (m, 4H), 1.03–0.87 (m, 1H), 1.01 (s, 3H), 0.85 ppm (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=170.8$, 165.2, 163.1, 135.8, 134.0, 131.6, 129.5, 127.5, 124.4, 113.4, 85.6, 84.2, 78.0, 73.1, 66.1, 63.9, 62.2, 55.4, 50.7, 50.5, 49.0, 47.2, 45.4, 37.1, 36.1, 34.5, 33.2, 32.3, 26.8, 24.9, 21.6, 21.3, 18.8, 16.1 ppm; EIMS: m/z (%): 725 [M-H_2O-C_4H_9], 135; HREIMS: m/z (%) calcd for $C_{42}H_{49}O_9Si$: 725.3146 [M-H_2O-C_4H_9]; found: 725.3152± 0.0022.

Ac_2O (6 mg, 0.05 mmol) was added to a mixture of the above primary TBDPS ether **87** (10 mg, 0.01 mmol), pyridine (3 mg, 0.1 mmol) and DMAP (0.5 mg) in CH_2Cl_2 (0.5 mL) at 0°C. The reaction mixture was stirred at 40°C for 24 h before the addition of H_2O at 0°C and extraction with EtOAc (3×2 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (35% EtOAc/hexane) to give **88** (7 mg, 65%). $[\alpha]_D^{20}=+6.00$ ($c=0.5$, $CHCl_3$); IR (NaCl): $\tilde{\nu}=$ 3396.3, 2963.4, 2939.1, 2859.8, 1737.8, 1609.8, 1384.1, 1286.6, 1262.2, 1097.6, 1024.4 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta=7.91$ (d, 1H, $J=$ 8.78 Hz), 7.71–7.65 (m, 4H), 7.51–7.34 (m, 6H), 6.91 (d, 1H, $J=8.78$ Hz), 6.27 (t, 1H, $J=3.02$ Hz), 5.33–5.41 (m, 1H), 5.12 (dt, 1H, $J=10.98$, 4.39 Hz), 5.09 (d, 1H, $J=12.08$ Hz), 4.61 (s, 1H, OH), 4.57 (1H, $J=$ 12.08 Hz), 4.21 (s, 1H, OH), 3.86 (s, 3H), 3.74 (dd, 1H, $J=10.70$, 1.37 Hz), 3.40 (dd, 1H, $J=10.70$, 3.57 Hz), 2.47–2.26 (m, 4H), 2.20 (s, 3H), 2.07–1.87 (m, 6H), 1.86–1.64 (m, 4H); 1.82 (s, 3H), 1.68 (s, 3H), 1.60–1.50 (m, 1H), 1.40–1.20 (m, 2H), 1.17 (s, 3H). 1.09 ppm (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=170.80$, 169.77, 169.57, 165.14, 163.59, 135.90, 135.68, 131.25, 130.02, 127.83, 122.27, 113.93, 81.89, 73.28, 71.77, 70.89, 68.69, 64.04, 61.40, 55.45, 50.79, 47.65, 47.40, 44.97, 43.67, 39.20, 35.98, 34.72, 33.23, 28.23, 26.82, 23.18, 21.60, 21.46, 21.06, 20.53, 19.16, 15.51 ppm; EIMS: m/z (%): 809 [M-H_2O-C_4H_9], 199; HREIMS: m/z (%) calcd for $C_{50}H64_{53}O_{12}Si$: 809.3357 [M-H_2O-C_4H_9]; found: 809.3367± 0.0024.

94: TBAF (1M solution, 0.08 mL, 0.084 mmol) was added to compound **88** (50 mg, 0.056 mmol) in THF (0.5 mL) at 0°C and stirred at the same temperature for 2 h. The reaction mixture was then quenched with saturated ammonium chloride solution and extracted with $EtOA_C$ (3×1 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (80% EtOAc/hexane) to afford the corresponding alcohol (32 mg, 90%). $[\alpha]_D^{20}=+9.60$ ($c=1.5$, $CHCl_3$); IR (NaCl): $\tilde{\nu}=3567.1$, 3390.2, 2963.4, 2932.9, 1731.7, 1603.7, 1384.1, 1286.6, 1256.1, 1091.5, 1030.5 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta=7.91$ (d, 2H, $J=9.06$ Hz), 6.91 (d, 2H, $J=9.06$ Hz), 6.27 (d, 1H, $J=2.74$ Hz), 5.40–5.32 (m, 1H), 5.12 (dt, 1H, $J=8.23$, 4.12 Hz), 5.09 (d, 1H, $J=12.08$ Hz), 4.51 (d, 1H, $J=12.08$ Hz), 4.20 (s, 1H, OH), 3.86 (s, 3H), 3.80 (dd, 1H, $J=10.70$, 2.20 Hz), 3.54 (dd, 1H, $J=10.70$, 3.02 Hz), 2.46–2.34 (m, 2H), 2.30–2.13 (m, 2H), 2.22 (s, 3H), 2.09–1.78 (m, 8H), 1.82 (s, 3H), 1.77–1.51 (m, 3H), 1.68 (s, 3H), 1.41–1.20 (m, 2H), 1.13 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=170.87$, 169.80, 169.55, 165.12, 163.61, 131.24, 122.20, 113.95, 82.43, 73.17, 71.61, 70.78, 68.61, 62.16, 61.34, 55.45, 50.39, 47.65, 47.34, 45.02, 43.71, 39.52, 35.94, 34.65, 33.04, 29.69, 28.21, 23.16, 21.60, 21.52, 21.06, 20.53, 15.19 ppm; EIMS: m/z (%): 628 [M-H_2O], 135; HREIMS: m/z (%) calcd for $C_{34}H_{44}O_{11}$: 628.2883 [M-H_2O]; found: 628.2895± 0.0019.

To a solution of the above alcohol (25 mg, 0.038 mmol) in CH_2Cl_2 (1 mL) at 0°C, Dess–Martin periodinane (32 mg, 0.077 mmol) was added and the solution was allowed to warm to RT. The solution was stirred for 45 min and was then quenched with Na_2SO_4-doped saturated $NaHCO_3$ solution. The mixture was extracted with EtOAc (3×1 mL) and the combined layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (50% EtOAc/hexane) to afford **94** (18 mg, 75%). $[\alpha]_D^{20}=+19.36$ ($c=1.1$, $CHCl_3$); IR (NaCl): $\tilde{\nu}=3573.2$, 3023.6, 2943.6, 1737.8, 1369.7, 1252.3, 1097.6 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta=9.77$ (d, 1H, $J=3.02$ Hz), 7.90 (d, 2H, $J=8.78$ Hz), 6.91 (d, 2H, $J=8.79$ Hz), 6.23 (t, 1H, $J=$ 2.74 Hz), 5.40–5.33 (m, 1H), 5.17 (dt, 1H, $J=10.70$, 4.94 Hz), 5.07 (d, 1H, $J=12.62$ Hz), 4.49 (d, 1H, $J=12.62$ Hz), 4.21 (s, 1H, OH), 3.86 (s, 3H), 2.48–2.31 (m, 3H), 2.30–2.08 (m, 4H), 2.23 (s, 3H), 2.04–1.87 (m, 4H), 1.87–1.78 (m, 2H), 1.83 (s, 3H), 1.68 (s, 3H), 1.65–1.53 (m, 2H), 1.37–1.22 (m, 2H), 1.19 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=$ 205.49, 170.87, 169.67, 169.50, 165.05, 163.67, 131.24, 122.09, 113.97, 83.69, 73.10, 70.52, 68.47, 61.21, 60.79, 55.46, 50.17, 47.36, 43.90, 43.24, 39.43, 35.91, 34.51, 33.29, 28.19, 23.13, 21.50, 21.04, 20.52, 19.80, 15.40 ppm; EIMS: m/z (%): 644 [M^+] 107; HREIMS: m/z (%) calcd for $C_{34}H_{44}O_{12}$: 644.2833 [M^+]; found: 644.2839±0.0019.

95: To a stirred mixture of the aldehyde **94** (10 mg, 0.015 mmol), Wilkinson's catalyst (0.4 mg, 4.6×10^{-4} mmol), Ph_3P (4.4 mg, 0.017 mmol), *i*PrOH(1.8 mg, 0.03 mmol) and THF (0.5 mL), $TMSCHN_2$ (3.4 mg, 0.03 mmol) were added and the reaction mixture was stirred for 16 h at ambient temperature. The reaction mixture was concentrated under vacuum and the residue was purified by silica gel flash chromatography (50% EtOAc/hexane) to afford the olefin **95** (6 mg, 67% yield). $[\alpha]_D^{20}=$ +9.3 ($c=0.5$, $CHCl_3$); IR (NaCl): $\tilde{\nu}=3571$, 3018, 2958, 2931, 1732, 1705, 1609, 1385, 1097, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta=7.90$ (d,

2H, J=9.06 Hz), 6.92 (d, 2H, J=9.06 Hz), 6.26 (t, 1H, J=2.74 Hz), 6.00–5.85 (m, 1H), 5.39–5.31 (m, 1H), 5.10 (dt, 1H, J=9.61, 4.39 Hz), 5.05 (d, 1H, J=12.08 Hz), 4.94–4.82 (m, 2H), 4.50 (d, 1H, J=12.08 Hz), 4.21 (s, 1H, OH), 3.86 (s, 3H), 2.47–2.32 (m, 2H), 2.29–1.98 (m, 5H), 2.23 (s, 3H), 1.97–1.80 (m, 3H), 1.83 (s, 3H), 1.79–1.54 (m, 5H), 1.68 (s, 3H), 1.38–1.19 (m, 2H), 1.00 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ= 170.9, 169.7, 169.5, 163.6, 143.0, 131.2, 122.1, 113.95, 113.91, 84.6, 73.1, 71.3, 70.6, 68.5, 61.2, 55.4, 54.8, 48.0, 47.3, 44.2, 43.9, 40.5, 35.9, 34.6, 32.7, 29.7, 28.1, 26.5, 22.9, 21.5, 21.0, 20.5, 16.0 ppm; EIMS: m/z (%): 642 [M^+], 624 [M-H_2O], 135; HREIMS: m/z (%) calcd for $C_{35}H_{46}O_{11}$: 642.3040 [M^+]; found: 642.3029±0.0019.

93: 4-Methylmorpholine *N*-oxide (3.6 mg, 0.03 mmol) and a solution of OsO_4 in H_2O (4% in H_2O, 0.02 mL, 0.003 mmol) were added to a stirred solution of olefin **95** (10 mg, 0.015 mmol) in acetone/water (20:1, 0.4 mL) and the resulting solution was stirred for 5 h at RT. After addition of sodium hydrogen sulphate solution, the mixture was further stirred for 30 min at the same temperature and extracted with EtOAc (3×2 mL). The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue which on silica gel column chromatography (EtOAc) afforded the corresponding diol (8 mg, 82%). IR (NaCl): $\tilde{\nu}$= 3573.2, 3397.1, 3013.1, 2959.6, 2932.9, 1737.8, 1609.8, 1513.7, 1385.7, 1369.7, 1097.6, 1033.5 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.91 (d, 2H, J=8.51 Hz), 6.91 (d, 2H, J=8.51 Hz), 6.27–6.20 (m, 1H), 5.39–5.32 (m, 1H), 5.18–5.02 (m, 2H), 4.51 (d, 1H, J=12.62 Hz), 4.20 (s, 1H, OH), 4.12 (brs, 1H, OH), 3.86 (s, 3H), 3.79–3.71 (m, 1H), 3.66–3.43 (m, 2H), 2.46–2.31 (m, 2H), 2.29–2.11 (m, 2H), 2.23 (s, 3H), 2.10–1.50 (m, 11H), 1.82 (s, 3H), 1.68 (s, 3H), 1.39–1.18 (m, 2H), 1.24 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=171.01, 169.86, 169.76, 169.56, 165.01, 163.63, 131.24, 127.79, 122.15, 113.96, 83.44, 82.62, 77.22, 76.82, 73.18, 72.93, 71.51, 71.09, 70.71, 70.41, 68.60, 68.37, 65.78, 61.36, 60.97, 55.46, 51.14, 50.29, 47.98, 47.34, 46.02, 45.07, 43.69, 43.58, 39.37, 39.25, 35.91, 34.68, 33.14, 32.58, 29.69, 28.33, 28.19, 25.59, 23.21, 21.57, 21.43, 21.21, 21.06, 20.72, 20.55, 18.54, 16.85, 15.41 ppm; EIMS: m/z (%): 658 [M-H_2O], 135; HREIMS: m/z (%) calcd for $C_{35}H_{46}O_{12}$: 658.2989 [M-H_2O]; found: 658.2985±0.0020.

A mixture of the above diol (70 mg, 0.1 mmol) and dibutyl tin oxide (51 mg, 0.2 mmol) in benzene (1 mL) was refluxed for 16 h in a Dean–Stark apparatus. The solvent was removed under reduced pressure and the residue of **96** was dissolved in $CHCl_3$ (1 mL). Molecular sieves 4 Å and NBS (38 mg, 0.2 mmol) were added and the mixture was stirred for 10 min at RT. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel flash chromatography (70% EtOAc/hexane) to afford the hydroxyl ketone **93** (50 mg, 73%) as a somewhat unstable sticky material. IR (NaCl): $\tilde{\nu}$=3379, 3063, 3018, 2986, 1737, 1700, 1591, 1486, 1252, 1175, 1028 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.92 (d, 2H, J=8.78 Hz), 6.91 (d, 2H, J=8.78 Hz), 6.25 (t, 1H, J=3.29 Hz), 5.39–5.33 (m, 1H), 5.12 (dt, 1H, J=10.94, 4.10 Hz), 5.11 (d, 1H, J=12.08 Hz), 4.47 (d, 1H, J=12.08 Hz), 4.37 (s, 1H, OH), 4.31 (d, 1H, J=4.39 Hz), 4.29 (d, 1H, J=4.39 Hz), 4.19 (s, 1H, OH), 3.86 (s, 3H), 3.01 (brs, 1H, OH), 2.77 (dd, 1H, J= Hz), 2.90–2.17 (m, 5H), 2.24 (s, 3H), 2.17–2.04 (m, 2H), 2.02–1.87 (m, 5H), 1.81 (s, 3H), 1.68 (s, 3H), 1.66–1.52 (m, 2H), 1.36–1.19 (m, 2H), 1.04 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=170.69, 169.8, 169.5, 165.1, 163.6, 133.1, 131.2, 122.1, 113.9, 83.4, 73.0, 70.9, 70.5, 70.1, 68.5, 61.2, 56.8, 49.3, 47.3, 43.9, 43.4, 39.0, 35.9, 34.6, 34.2, 29.6, 28.2, 24.7, 23.2, 21.5, 21.0, 20.4, 15.5 ppm; EIMS: m/z (%): 656 [M-H_2O], 135; HREIMS: m/z (%) calcd for $C_{35}H_{44}O_{12}$: 656.2833 [M-H_2O]; found: 656.2825±0.0020.

92: Triphenylphosphoranylidene ketene (14 mg, 0.044 mmol) was added to a mixture of the hydroxyl ketone **93** (15 mg, 0.022 mmol), triethylamine (11 mg, 0.11 mmol), and benzene (0.5 mL) at RT and the mixture was stirred at RT for 24 h. The reaction mixture was concentrated and the residue was directly purified by flash chromatography on silica gel (50% EtOAc/hexane) to give **92** (11 mg, 68%) as a white solid. M.p.: 108°C; $[\alpha]_D^{20}$=+28.23 (c=0.5, $CHCl_3$); IR (NaCl): $\tilde{\nu}$=3575.6, 3038.1, 2920.7, 1746.3, 1604.9, 1370.7, 1263.4 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.89 (d, 2H, J=9.06 Hz), 6.91 (d, 2H, J=9.06 Hz), 6.24 (t, 1H, J= 2.74 Hz), 5.91 (brs, 1H), 5.38–5.32 (m, 1H), 5.09 (dt, 1H, J=10.98, 4.12 Hz), 5.06 (d, 1H, J=12.35 Hz), 4.93 (dd, 1H, J=18.39, 1.92 Hz), 4.79 (dd, 1H, J=18.39, 1.65 Hz), 4.47 (d, 1H, J=12.35 Hz), 4.20 (s, 1H, OH), 3.36 (s, 3H), 2.78 (dd, 1H, J=9.06, 4.94 Hz), 2.46–2.30 (m, 2H), 2.29–2.06 (m, 4H), 2.23 (s, 3H), 2.00–1.79 (m, 6H), 1.81 (s, 3H), 1.77–1.59 (m, 2H); 1.68 (s, 3H), 1.77–1.20 (m, 2H), 1.00 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=174.28, 173.28, 170.90, 169.74, 169.52, 165.03, 163.068, 131.23, 122.04, 118.24, 113.98, 84.22, 73.42, 73.03, 71.02, 70.46, 68.45, 61.16, 55.47, 50.02, 49.47, 47.32, 44.94, 43.86, 40.19, 35.87, 34.51, 33.20, 28.18, 26.75, 23.13, 21.50, 21.04, 20.52, 16.13 ppm; EIMS: m/z (%): 698 [M^+], 135; HREIMS: m/z (%) calcd for $C_{37}H_{46}O_{13}$: 698.2938 [M^+]; found: 698.2955±0.0021.

1b: The compound **92** (50 mg, 0.071 mmol) in MeOH (1 mL) and saturated Na_2CO_3 solution (0.1 mL) was stirred for 1 h at RT and the reaction was quenched by the addition of 1N HCl until pH 6. The mixture was then extracted with 2:1 $CHCl_3$ and EtOH (5×2 mL) and the combined extracts were washed with brine. The organic layer was concentrated in vacuo and the crude product was flashed on silica gel (20–30% MeOH in CH_2Cl_2) to get ouabagenin **1b** (27 mg, 85%) as a white solid. M.p.:185–188; IR (KBr): $\tilde{\nu}$=3457, 3243, 2945, 2878, 1725, 1646, 1615, 1445, 1207, 1048 cm^{-1}; ^{1}H NMR (CD_3OD, 300 MHz): δ=5.91 (brs, 1H, olefinic proton), 5.01 (dd, 1H, J=18.39, 1.37 Hz), 4.91 (dd, 1H, J=18.39, 1.92 Hz), 4.88–4.84 (m, 1H), 4.36 (d, 1H, J=11.53 Hz), 4.31–4.21 (m, 1H), 4.16 (d, 1H, J=11.53 Hz), 4.11–3.94 (m, 1H), 2.91 (dd, 1H, J=9.06, 4.94 Hz), 2.23–2.05 (m, 4H), 2.04–1.82 (m, 3H), 1.78–1.64 (m, 3H), 1.63–1.42 (m, 4H), 1.39–1.21 (m, 2H), 0.94 ppm (s, 3H); ^{13}C NMR (DMSO:$CDCl_3$(2:1), 75 MHz): δ=175.56, 174.11, 116.82, 84.01, 79.36, 75.61, 73.47, 66.73, 65.94, 61.11, 50.24, 49.51, 49.10, 48.88, 47.66, 46.21, 40.56, 35.11, 32.83, 31.00, 26.56, 23.13, 17.41 ppm; ESIMS: m/z (%): 461.13 [M+Na] (100%); EIMS: m/z (%): 420 [M-H_2O], 105; HREIMS: m/z (%) calcd for $C_{23}H_{32}O_7$: 420.2148 [M-H_2O]; found: 420.2151±0.0013.

101: The diacetate **89** (400 mg, 0.71 mmol) in MeOH (3 mL) and saturated Na_2CO_3 solution (0.2 mL) was stirred for 1 h at RT and the reaction was quenched by the addition of 1N HCl until pH 6. The mixture was then extracted with CH_2Cl_2 (3×3 mL) and the combined extracts were washed with brine. The organic layer was concentrated in vacuo and the crude product was flashed on silica gel (10% MeOH in CH_2Cl_2) to get the alcohol **101** (260 mg, 70%) as a white solid. M.p.: 99–101°C; $[\alpha]_D^{20}$= +20.8 (c=4.3, $CHCl_3$); IR (NaCl): $\tilde{\nu}$=3470, 3008, 2940, 1738, 1742, 1444, 1385 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=5.87 (brs, 1H), 5.26 (dt, 1H, J=9.3, 4.9 Hz), 4.95 (dd, 1H, J=18.1, 1.0 Hz), 4.92 (brs, 1H), 4.77 (dd, 1H, J=18.1, 1.0 Hz), 4.43 (d, 1H, J=12.6 Hz), 4.40 (t, 1H, J=3.29 Hz), 4.19 (m, 1H), 3.97 (d, 1H, J=12.6 Hz), 3.67 (d, 1H, OH, J=7.6 Hz), 2.80 (dd, 1H, J=9.3, 6.0 Hz), 2.18–1.99 (m, 4H), 2.05 (s, 1H, 3H), 1.99–1.60 (m, 6H), 1.54–1.34 (m, 5H), 1.39 (s, 3H), 1.36 (s, 3H), 1.26–1.09 (m, 1H), 0.94 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=174.58, 173.68, 169.57, 117.76, 99.80, 83.07, 76.76, 75.31, 73.51, 72.04, 70.94, 69.59, 68.41, 66.57, 61.30, 49.81, 48.83, 43.88, 43.66, 43.41, 39.49, 37.26, 37.20, 32.91, 32.35, 26.56, 26.39, 23.88, 21.45, 20.80, 16.62 ppm; EIMS: m/z (%): 505 [M-CH_3^+], 384. HREIMS: m/z (%) calcd for $C_{27}H_{37}O_9$: 505.2437 [M-CH_3^+]; found: 505.2428.

102: A mixture of alcohol **101** (100 mg, 0.16 mmol) and 4 Å molecular sieves in CH_2Cl_2 (2 mL) was stirred for 10 min at RT and then cooled to 0°C. A solution of imidate **100** (142 mg, 0.17 mmol) in CH_2Cl_2 (0.5 mL) was added and the mixture was stirred for an additional 10 min. TMSOTf (13 μL, 0.04 mmol) diluted in CH_2Cl_2 (100 μL) was then added and the reaction was left at RT over a period of 20 min and then stirred for 2 h. It was then quenched with H_2O, extracted with CH_2Cl_2 (3× 2 mL), and the combined extracts were washed with brine and dried over anhydrous Na_2SO_4. After concentration in vacuo, the crude product was purified on silica gel (EtOAc) to get **102** (190 mg, 90%) as a solid. M.p.: 172°C; $[\alpha]_D^{20}$=+84.3 (c=1.7, $CHCl_3$); IR (NaCl): $\tilde{\nu}$=3524, 3025, 2934, 1786, 1731, 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=8.13–8.06 (m, 2H), 7.97–7.90 (m, 2H), 7.83–7.80 (m, 2H), 7.66–7.61 (m, 1H), 7.56–7.49 (m, 3H), 7.45–7.37 (m, 3H), 7.29–7.23 (m, 2H), 5.89 (brs, 1H), 5.79 (dd, 1H, J=10.4, 3.2 Hz), 5.69 (t, 1H, J=9.8 Hz), 5.63 (dd, 1H, J=3.2, 1.6 Hz), 5.33 (dt, 1H, J=9.3, 5.9 Hz), 5.17 (d, 1H, J=1.6 Hz), 4.86 (dd, 1H, J=18.1, 1.6 Hz), 4.78 (dd, 1H, J=18.1, 1.6 Hz), 4.65–4.57 (m, 2H), 4.63 (s, 1H, OH), 4.42 (brs, 1H), 4.26 (brs, 1H), 3.77 (d, 1H, J= 12.6 Hz), 2.85 (t, 1H, J=8.2 Hz), 2.36–2.26 (m, 1H), 2.19–2.01 (m, 3H),

2.06 (s, 3H), 2.00–1.87 (m, 3H), 1.82–1.44 (m, 8H), 1.57 (s, 3H), 1.35 (d, 3H, J=5.9 Hz), 1.30 (s, 3H), 1.29–1.06 (m, 1H), 0.98 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=174.03, 172.43, 169.11, 165.81, 165.63, 165.17, 133.49, 133.35, 133.00, 129.90, 129.67, 129.61, 129.45, 129.30, 128.60, 128.45, 128.23, 122.35, 118.07, 101.13, 98.20, 83.47, 75.09, 73.28, 72.79, 71.93, 71.47, 70.43, 69.66, 66.95, 66.83, 60.50, 49.70, 48.67, 47.38, 43.91, 43.50, 40.92, 35.95, 35.59, 33.64, 30.24, 26.61, 24.68, 23.15, 23.08, 21.54, 17.50, 16.97.2 ppm; ESIMS: m/z (%): 1017.15 [M+Na^+], 1001.17 [M+K^+].

1a: The glycoside **102** (40 mg, 0.04 mmol) in MeOH (1 mL) was treated with 1 N HCl (0.1 mL) at RT for 2 h. The mixture was concentrated under *vacuo* and the crude product was flashed on silica gel (10% MeOH in CH_2Cl_2) to get the corresponding deacetonide product (35 mg, 92%) as a white solid. M.p.: 178–180 °C; $[\alpha]_D^{20}$=+50.5 (c=3.5, $CHCl_3$); IR (NaCl): $\tilde{\nu}$=3498, 3008, 2963, 1783, 1728, 1458, 1261, 1106, 1069 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=8.04–7.93 (m, 4H), 7.84–7.76 (m, 2H), 1.02–7.25 (m, 9H), 5.84 (dd, 1H, J=10.05, 3.02), 5.81–5.73 (m, 2H), 5.68 (1H, t, J=10.05 Hz), 5.34 (dt, 1H, J=9.61, 4.39 Hz), 5.21 (d, 1H, J=1.37 Hz),4.80 (d, 1H, J=17.56 Hz), 4.79 (brs, 1H), 4.66 (d, 1H, J=17.56 Hz), 4.54 (d, 1H, J=11.25 Hz), 4.45–4.33 (m, 2H), 3.85 (brs, 3H, OH), 2.67–2.58 (dd, 1H, J=9.06, 4.94 Hz), 2.49–2.21 (m, 2H), 2.18–1.59 (m, 11H), 2.01 (s, 3H), 1.48–1.39 (m, 1H), 1.38 (d, 3H, J=6.31 Hz), 1.30–1.11 (m, 2H), 0.46 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=174.37, 173.68, 169.43, 166.53, 166.27, 165.80, 133.90, 133.44, 133.38, 129.89, 129.82, 129.76, 129.67, 128.83, 128.75, 128.57, 128.49, 128.44, 117.78, 94.88, 84.12, 77.27, 74.99, 73.42, 71.43, 71.33, 71.19, 70.92, 70.23, 67.04, 60.61, 49.89, 49.30, 47.73, 44.53, 44.39, 40.11, 35.98, 34.13, 32.71, 32.27, 26.74, 23.50, 21.62, 17.78, 15.89 ppm; ESIMS: m/z (%): 939.24 [M+H^+], 961.18 [M+Na^+], 977.12 [M+K^+].

A mixture of the above deacetonide product (28 mg, 0.029 mmol) in MeOH (1 mL) and saturated Na_2CO_3 solution (0.1 mL) was stirred for 1 h at RT and the reaction was quenched by the addition of 1 N HCl until pH 6. The mixture was then extracted with 2:1 $CHCl_3$ and EtOH (5× 2 mL) and the combined extracts were washed with brine. The organic layer was concentrated in vacuo and the crude product was flashed on silica gel (15–20% MeOH in CH_2Cl_2) to get ouabain **1a** (15 mg, 88%) as a white solid. M.p.: 185–187 °C; $[\alpha]_D^{20}$=−30.6 (c=0.5, MeOH), $[\alpha]_D^{20}$ (sample from Sigma–Aldrich company)=−36.8 (c=1, MeOH); IR (KBr film): $\tilde{\nu}$=3375, 2942, 1735, 1632, 1426 cm^{-1}, 1056; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=5.91 (s, 1H), 4.99 (dd, 1H, J=18.1, 1.0 Hz), 4.89 (dd, 1H, J=18.1, 1.0 Hz), 4.84 (d, 1H, J=1.6 Hz), 4.41 (d, 1H, J=11.5 Hz), 4.24 (brs, 1H), 4.15 (d, 1H, J=11.5 Hz), 4.10 (brs, 1H), 3.76 (dd, 1H, J=3.2, 1.6 Hz), 3.71 (dq, 1H, J=9.3, 6.5 Hz), 3.68 (dd, 1H, J=9.3, 3.2 Hz), 3.37 (t, 1H, J=9.3 Hz), 2.91 (dd, 1H, J=8.2, 6.5 Hz), 2.29–2.04 (m, 4H), 1.99–1.84 (m, 4H), 1.77–1.67 (m, 3H), 1.59–1.39 (m, 4H), 1.31–1.24 (m, 1H), 1.26 (d, 3H, J=6.5 Hz), 0.94 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=176.17, 175.70, 116.59, 97.77, 84.30, 73.88, 72.73, 71.11, 70.90, 70.09, 68.70, 68.53, 67.41, 60.25, 50.22, 49.46, 48.75, 48.42, 48.26, 47.16, 47.12, 47.08, 39.64, 32.12, 26.38, 22.72, 16.58, 16.07 ppm; ESIMS: m/z (%): 585.27 [M+H^+], 607.24 [M+Na^+], 623.23 [M+K^+]; HREIMS: m/z (%) calcd for $C_{29}H_{42}O_{11}$: 566.2727 [M-H_2O^+]; found: 566.2734.

Acknowledgements

We thank NSERCC (Ottawa) for financial support.

[1] R. Thomas, P. Gray, J. Andrew, *Adv. Drug Res.* **1990**, *19*, 312–562.
[2] For a review of cardiac glycosides, see P. S. Steyn, F. R. Heerden, *Nat. Prod. Rep.* **1998**, 397–413.
[3] a) L. F. Fieser, M. Fieser, *Steroids*; Reinhold, New York, **1959**, chap. 20; b) A. Arnaud, *Compt. Rendu* **1888**, *106*, 1011; A. Arnaud, *Compt. Rendu* **1888**, *107*, 1162.
[4] a) A. Szent-Gyorgyi, *Chemical Physiology of Contraction in Body and Heart Muscle*, Academic Press, New York, **1953**, pp. 86–91; b) W. Schoner, *Eur. J. Biochem.* **2002**, *269*, 2440–2448.
[5] a) S. M. Hamlyn, M. P. Blaustein, S. Boua, D. W. Du Charme, D. W. Harris, F. Mandel, W. R. Mathews, S. H. Ludens, *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 6259–6263; b) A. Kawamura, J. Guo, Y. Itagaki, C. Bell, Y. Wang, H. T. Garner, S. Magil, R. T. Gallagher, N. Berova, K. Nakanishi, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 6654–6659; c) A. Kawamura, J. Guo, F. Maggiali, N. Berova, K. Nakanishi, *Pure Appl. Chem.* **1999**, *71*, 1643–1648; d) B. C. Hong, S. Kim, T.-S. Kim, E. J. Corey, *Tetrahedron Lett.* **2006**, *47*, 2711–2715.
[6] a) C. Mannich, G. Siewert, *Ber.* **1942**, *75*, 737 and 750; b) K. Florey, M. Ehrenstein, *J. Org. Chem.* **1954**, *19*, 1174–1192.
[7] a) S. Laschat, F. Narjes, L. E. Overman, *Tetrahedron* **1994**, *50*, 347–358; b) W. Deng, M. S. Jensen, L. E. Overman, P. V. Rucker, J.-P. Vionnet, *J. Org. Chem.* **1996**, *61*, 6760–6761; c) P. V. Rucker, L. E. Overman, *Tetrahedron Lett.* **1998**, *39*, 4643–4646; d) J. H. Hynes, L. E. Overman, T. Nasser, P. V. Rucker, *Tetrahedron Lett.* **1998**, *39*, 4647–4650; e) L. E. Overman, P. V. Rucker, *Heterocycles* **2000**, *52*, 1297–1314.
[8] a) M. E. Jung, P. Davidov, *Angew. Chem.* **2002**, *114*, 4299–4302; *Angew. Chem. Int. Ed.* **2002**, *41*, 4125–4128; b) M. E. Jung, G. Piizzi, *J. Org. Chem.* **2003**, *68*, 2572–2582; c) M. E. Jung, G. Piizzi, *Org. Lett.* **2003**, *5*, 137–140.
[9] For a review on enantioselective synthesis of steroids: A.-S. Chapelon, D. Maraleda, R. Rodriguez, C. Ollivier, M. Santelli, *Tetrahedron* **2007**, *63*, 11511–11616.
[10] a) J. F. Lavallée, P. Deslongchamps, *Tetrahedron Lett.* **1988**, *29*, 6033–6036; b) R. Ruel, P. Deslongchamps, *Tetrahedron Lett.* **1990**, *31*, 3961–3967; c) R. Ruel, P. Deslongchamps, *Can. J. Chem.* **1992**, *70*, 1939–1949.
[11] a) D. Chapdelaine, J. Belzile, P. Deslongchamps, *J. Org. Chem.* **2002**, *67*, 5669–5672; b) Z. Yang, D. Shannon, V.-L. Truong, P. Deslongchamps, *Org. Lett.* **2002**, *4*, 4693–4696; c) L. Chen, P. Deslongchamps, *Can. J. Chem.* **2005**, *83*, 728–740.
[12] H. Zhang, M. Sridhar Reddy, S. Phoenix, P. Deslongchamps, *Angew. Chem.* **2008**, *120*, 1292–1295; *Angew. Chem. Int. Ed.* **2008**, *47*, 1272–1275.
[13] S. Trudeau, P. Deslongchamps, *J. Org. Chem.* **2004**, *69*, 832–838.
[14] **24** is not stable and undergoes polymerization if concentrated.
[15] S. Krishnamurthy, *J. Org. Chem.* **1981**, *46*, 4628–4629.
[16] Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011–1013.
[17] L. N. Mander, S. P. Sethi, *Tetrahedron Lett.* **1984**, *25*, 5953–5956.
[18] M. S. Syamala, J. Das, S. Baskaran, S. Chandrasekaran, *J. Org. Chem.* **1992**, *57*, 1928–1930.
[19] J. A. R. Salvador, M. L. S. Melo, A. S. C. Neves, *Tetrahedron Lett.* **1996**, *37*, 687–690.
[20] a) A. L. Gemal, J. L. Luche, *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459; b) J. L. Luche, *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.
[21] J. H. Brewster, H. O. Bayer, *J. Org. Chem.* **1964**, *29*, 116–121.
[22] R. Budziarek, J. D. Johnston, W. Manson, F. S. Spring, *J. Chem. Soc.* **1951**, 3019–3026.
[23] S. A. Ramachandran, R. K. Kharul, S. Marque, P. Soucy, F. Jacques, R. Chênevert, P. Deslongchamps, *J. Org. Chem.* **2006**, *71*, 6149–6156.
[24] "Reduction of Carboxylic Acid Derivatives to Alcohols, Ethers and Amines," A. G. M. Barrett, in *Comprehensive Organic Synthesis* (Ed.: B. M. Trost), **1991**, Vol. 8, pp. 244.
[25] P. G. Baraldi, A. Barco, S. Benetti, V. Ferretti, G. P. Pollini, E. Polo, V. Zanirato, *Tetrahedron* **1989**, *45*, 1517–1532.
[26] B. C. Barot, H. W. Pinnick, *J. Org. Chem.* **1981**, *46*, 2981–2983.
[27] A. K. Ghosh, H. Lei, *J. Org. Chem.* **2002**, *67*, 8783–8788.
[28] M. Hongu, N. Funami, Y. Takahashi, K. Saito, K. Arakawa, M. Matsumoto, H. Yamakita, K. Tsujihara, *Chem. Pharm. Bull.* **1998**, *46*, 1545–1555.
[29] L. A. Paquette, Z. Gao, Z. Ni, G. F. Smith, *J. Am. Chem. Soc.* **1998**, *120*, 2543–2552.
[30] R. M. Burk, M. B. Roof, *Tetrahedron Lett.* **1993**, *34*, 395–398.
[31] Y. Oikawa, T. Yoshioka, O. Yonemitsu, *Tetrahedron Lett.* **1982**, *23*, 889–892.
[32] N. Nakajima, K. Horita, R. Abe, O. Yonemitsu, *Tetrahedron Lett.* **1988**, *29*, 4139–4142.

[33] There are only two examples in the literature about the formation of orthoester by DDQ oxidation of PMB ether: a) D. A. Evans, D. H. B. Ripin, D. P. Halstead, K. R. Campos, *J. Am. Chem. Soc.* **1999**, *121*, 6816–6826; b) M. Lautens, R. K. Belter, *Tetrahedron Lett.* **1992**, *33*, 2617–2620.
[34] a) A. Kawamura, L. M. Abrell, F. Maggiali, N. Berova, K. Nakanishi, J. Labutti, S. Magil, G. T. Haupert, Jr., J. M. Hamlyn, *Biochemistry* **2001**, *40*, 5835–5844; b) R. Schneider, V. Wray, M. Nimtz, W. D. Lehmann, U. Kirch, R. Antolovic, W. Schoner, *J. Biol. Chem.* **1998**, *273*, 784–792; c) D. D. McIntyre, M. W. Germann, H. J. Vogel, *Can. J. Chem.* **1990**, *68*, 1263–1270.
[35] K. C. Nicolaou, M. Follmann, A. J. Roecker, K. W. Hunt, *Angew. Chem.* **2002**, *114*, 2207–2210; *Angew. Chem. Int. Ed.* **2002**, *41*, 2103–2106.
[36] C. K.-F. Chiu, S. V. Govindan, P. L. Fuchs, *J. Org. Chem.* **1994**, *59*, 311–323.
[37] P. Magnus, I. Sebhat, *J. Am. Chem. Soc.* **1998**, *120*, 5341–5342.
[38] Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011–1013.
[39] a) P. S. Wharton, D. H. Bohlen, *J. Org. Chem.* **1961**, *26*, 3615–3616; b) P. A. Zoretic, R. J. Chambers, G. Marbury, A. A. Riebiro, *J. Org. Chem.* **1985**, *50*, 2981–2987; c) M. J. Di Grandi, C. A. Coburn, R. C. A. Isaacs, S. J. Danishefsky, *J. Org. Chem.* **1993**, *58*, 7728–7731.
[40] A. Saito, A. Tanaka, T. Oritani, *Tetrahedron: Asymmetry* **1996**, *7*, 2923–2928.
[41] J. M. Finan, Y. Kishi, *Tetrahedron Lett.* **1982**, *23*, 2719–2722.
[42] a) B. Rajashekhar, E. T. Kaiser, *J. Org. Chem.* **1985**, *50*, 5480–5484; b) J. C. McWilliams, J. Clardy, *J. Am. Chem. Soc.* **1994**, *116*, 8378–8379.
[43] E. J. Corey, B. M. Stoltz, *Tetrahedron Lett.* **1999**, *40*, 2061–2064.
[44] P. A. Procopiou, S. P. D. Baugh, S. S. Flack, G. G. A. Inglis, *J. Org. Chem.* **1998**, *63*, 2342–2347.
[45] We also tried to protect ouabagenin as 1,11,19-trisacetates under several other conditions, but failed, see Ref. [36].
[46] a) I. Fleming, R. Hennings, H. Plaut, *J. Chem. Soc. Chem. Commun.* **1984**, 29–31; b) I. Fleming, P. E. J. Sanderson, *Tetrahedron Lett.* **1987**, *28*, 4229–4232; c) K. Tamao, N. Ishida, *J. Organomet. Chem.* **1984**, *269*, c37; d) K. Tamao, N. Ishida, T. Tanaka, M. Kumada, *Organometallics* **1983**, *2*, 1694–1696; e) K. Tamao, N. Ishida, M. Kumada, *Org. Chem.* **1983**, *48*, 2120–2122; f) G. R. Jones, *Tetrahedron* **1996**, *52*, 7599–7662 .
[47] Natural ouabain was obtained from Sigma–Aldrich company.
[48] R. P. A. Sneeden, R. B. Turner, *J. Am. Chem. Soc.* **1953**, *75*, 3510–3513.
[49] H. Lebel, D. Guay, V. Paquet, K. Huard, *Org. Lett.* **2004**, *6*, 3047–3050.
[50] a) F. D′Andrea, G. Catelani, M. Mariani, B. Vecchi, *Tetrahedron Lett.* **2001**, *42*, 1139–1142; b) A. B. C. Simas, K. C. Pais, A. A. T. da Silva, *J. Org. Chem.* **2003**, *68*, 5426–5428; and the references therein.
[51] a) H. J. Bestmann, D. Sandmeier, *Chem. Ber.* **1980**, *113*, 2038; b) G. Stork, F. West, H. Y. Lee, R. C. A. Isaacs, S. Manabe, *J. Am. Chem. Soc.* **1996**, *118*, 10660–10661.
[52] D. D. McIntyre, M. W. Germann, H. H. Vogel, *Can. J. Chem.* **1990**, *68*, 1263–1270.
[53] See Supporting Information.
[54] a) R. R. Schmidt, *Angew. Chem.* **1986**, *98*, 213–236; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 212–235; b) R. R. Schmidt, W. Kinzy, *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21–123; c) R. R. Schmidt, *Front. Nat. Prod. Res.* **1996**, *1*, 20–54; d) R. R. Schmidt, *Pure Appl. Chem.* **1989**, *61*, 1257–1270; e) A. Hölemann, B. L. Stocker, P. H. Seeberger, *J. Org. Chem.* **2006**, *71*, 8071–8088; f) K. Toshima, K. Tatsuta, *Chem. Rev.* **1993**, *93*, 1503–1531.

Received: November 14, 2008
Revised: January 19, 2009
Published online: March 17, 2009

