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A convergent total synthesis of ouabagenin†

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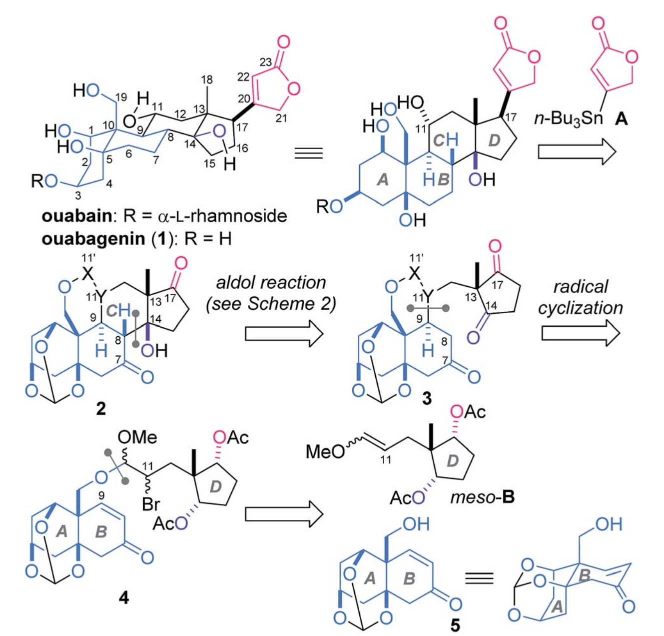
A convergent total synthesis of ouabagenin, an aglycon of cardenolide glycoside ouabain, was achieved by assembly of the AB-ring, D-ring and butenolide moieties. The multiply oxygenated *cis*-decalin structure of the AB-ring was constructed from (*R*)-perillaldehyde through the Diels–Alder reaction and sequential oxidations. The intermolecular acetal formation of the AB-ring and D-ring fragments, and combination of the intramolecular radical and aldol reactions, assembled the requisite steroidal skeleton in a stereoselective fashion. Finally, stereoselective installation of the C17-butenolide *via* the Stille coupling and hydrogenation led to ouabagenin.

Ouabain (Scheme 1), which belongs to a unique class of steroids known as cardenolides, has been used for the treatment of congestive heart failure for more than two centuries.[1,2] Ouabain was isolated from the bark and roots of the ouabaio tree, and was more recently identified as an adrenal hormone that naturally occurs in mammals.[3] The cardiac activity of ouabain is attributed to a high affinity inhibitory interaction with the membrane-bound sodium pump, Na^+/K^+-ATPase. As functional modulation of Na^+/K^+-ATPase activates multiple downstream signal transduction pathways, ouabain is implicated in the regulation of diverse physiological and pathological states. Importantly, cardenolides have received considerable attention for their preventive actions of proliferative diseases such as cancer.[4]



Scheme 1 Synthetic plan of ouabagenin (**1**).

The steroidal skeleton of ouabagenin (**1**, Scheme 1), an aglycon of ouabain, possesses six hydroxy groups and the β-oriented butenolide. This highly oxygenated structure of **1** has posed a formidable synthetic challenge.[5,6] Despite numerous synthetic studies on cardenolides, only two successful total syntheses of **1** have been reported to date. Deslongchamps constructed **1** through a polyanionic cyclization methodology and converted **1** to ouabain,[7] while Baran designed the redox relay strategy and efficiently transformed adrenosterone to **1**.[8] Motivated by the architectural complexity coupled with the valuable bioactivities, we have launched synthetic studies of cardenolides based on a distinctive convergent strategy.[9] Here we report the total synthesis of ouabagenin (**1**) by assembling the AB-ring fragment with the simple achiral D-ring and butenolide moieties.

The three-dimensional structure of **1** is disparate from the classical steroidal skeleton in that all the functional groups at the ring junctions (C5, 10, 13, 14) are β-configured (Scheme 1). This atypical ring fusion gives the nucleus a characteristic 'U' shape. The ring framework of **1** is further decorated by one primary (C19) and three secondary (C1, 3 and 11) hydroxy groups and an unsaturated lactone ring (C17). The congested disposition of these functionalities creates synthetic problems. To simplify the overall scheme, we retrosynthetically disassembled **1** into AB-ring **5**, D-ring *meso*-**B** and butenolide **A**. According to this plan, achiral **A**[10] and *meso*-**B**[9] were easily prepared, while introduction of only four out of ten stereocenters of **1** would be necessary for the synthesis of **5**. The

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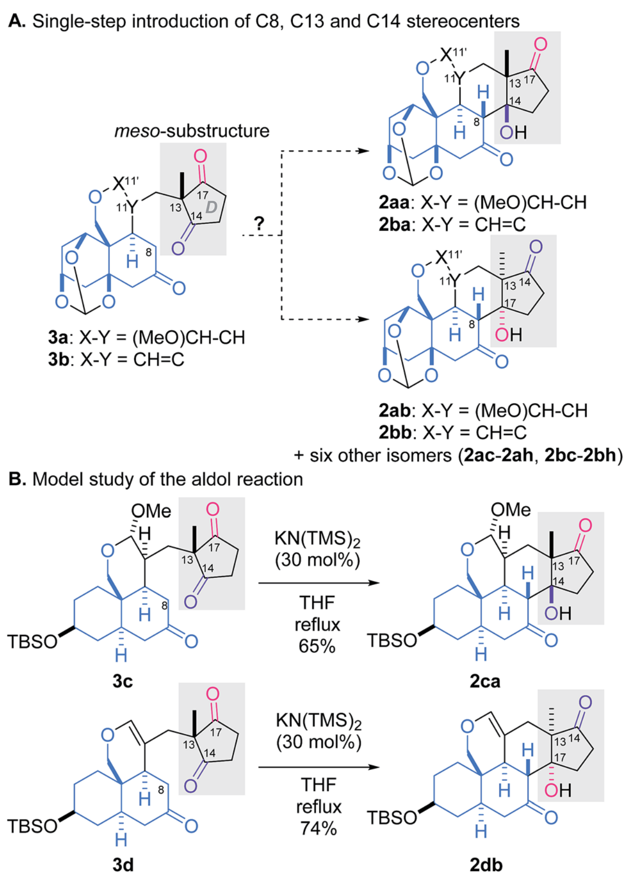
remaining six centers were planned to be installed en route to **1**. Most importantly, the stereochemistry of the four angular positions (C8, 9, 13, 14) was to be controlled by two intramolecular reactions. After tethering **5** and *meso*-**B** through the acetal linkage, 6-exo radical cyclization of **4** would establish the C9-stereochemistry. Aldol reaction of **3** would then be employed for simultaneous introductions of the C8-, 13- and 14-centers of **2**. The two peripheral functional groups at C11 and 17 were planned to be constructed from **2** at the last stage of the total synthesis.

It would be challenging to control the three stereocenters in the reaction from **3** to **2**: eight diastereomers would be potentially generated through desymmetrization of the *meso*-substructure (Scheme 2A).[11,12] We envisioned that the linker structure (X–Y) would affect the stereochemical outcome of the aldol reaction, and accordingly designed the two possible intermediates, acetal **3a** and vinyl ether **3b**, which would be integrated in the planned scheme. To assess suitability of **3a** or **3b** as the precursor, the relative energies of the eight isomers of each aldol reaction were evaluated *in silico*. The PM6 calculation indicated that two products (**2aa** and **2ab** from **3a**, **2ba** and **2bb** from **3b**) were thermodynamically more stable than the six other adducts.[13] However, selectivity between desired **2aa**/**2ba** and undesired **2ab**/**2bb** was not clarified by the simulation due to their small energy difference (<0.5 kcal mol^{-1}).



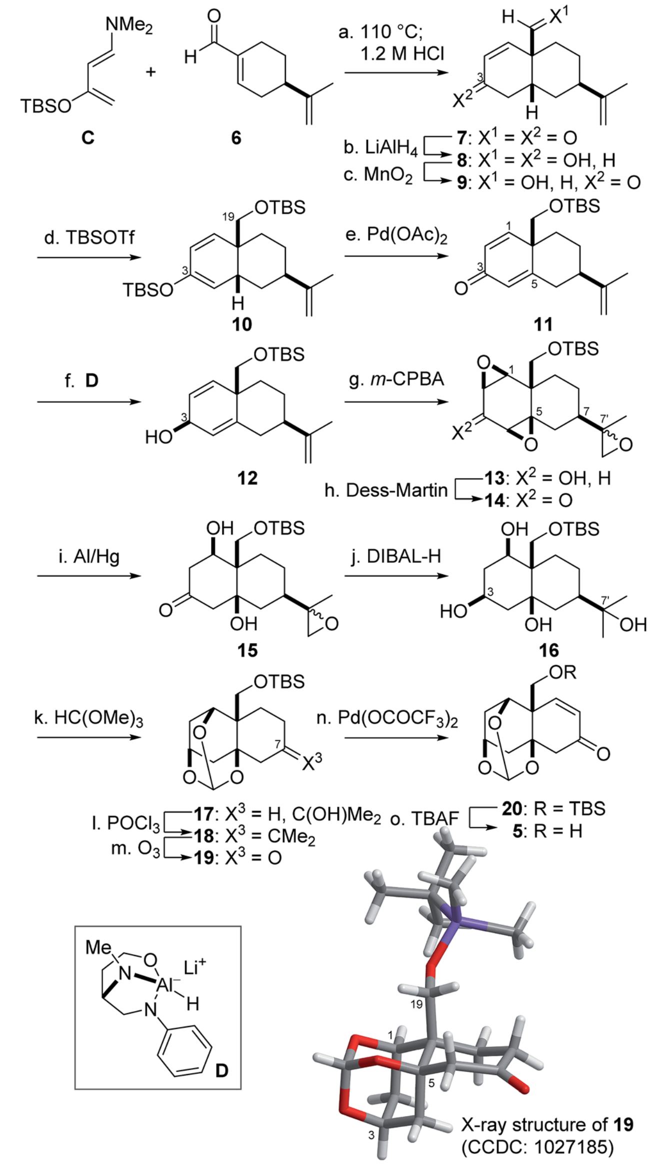
Scheme 2 Design of the substrates of Aldol reaction.

To experimentally examine the role of the linker (X–Y), the synthetically more accessible models **3c** and **3d** were prepared and subjected to the aldol reactions (Scheme 2B).[13] Despite their abbreviated structures, the *trans*-decalin rings of **3c** and **3d** were assumed to mimic the rigid orthoester-protected AB-ring of **3a** and **3b**, respectively. Treatment of acetal **3c** with catalytic $KN(TMS)_2$ in refluxing THF led to formation of desired **2ca** as the sole isolable isomer, whereas application of the same conditions to vinyl ether **3d** selectively afforded undesired **2db**. These results demonstrated the crucial function of the linker in influencing the stereoselectivity, and permitted us to target acetal **3a** as the key intermediate for the total synthesis.

Prior to the synthesis of **3a**, AB-ring **5** was prepared from (*R*)-perillaldehyde **6**[14] in 15 steps (Scheme 3). The Diels–Alder reaction between **6** and Rawal's diene **C**[15] proceeded in regio- and diastereoselective manner to afford the *cis*-decalin, which was treated with aqueous acid to provide **7** as a single product.[16] The two carbonyl groups of **7** were simultaneously reduced with $LiAlH_4$ to produce diol **8**, the allylic alcohol of which was chemoselectively oxidized with MnO_2 to provide ketone **9**. Treatment of **9** with TBSOTf and Et_3N then introduced the two TBS groups at the C3-enol and C19-hydroxy groups, resulting in **10**. $Pd(OAc)_2$-mediated oxidation[17] of **10** in turn provided dienone **11**.[18] For introduction of the β-configured C1- and 5-oxygen functional groups, the C3-β-alcohol was utilized as the directing group. Namely, ketone **11** was stereoselectively reduced by the action of the chiral reductant **D**[19] to produce **12** (dr = 3 : 1).[20] Thus obtained **12** was treated with *m*-CPBA to induce the requisite bis-β-epoxidation in addition to the epoxidation at C7′, leading to tris-epoxide **13**. After Dess–Martin oxidation[21] of alcohol **13** to ketone **14**, reductive opening of the two epoxides of **14** proximal to the C3-ketone was realized using Al/Hg[6g,22] to generate **15**. Next, DIBAL-H transformed **15** into tetraol **16** through stereoselective hydride attack on the C3-ketone from the opposite side of the C1,5-hydroxy groups and regioselective attack on the C7′-epoxide.

Having established the C1,3,5-stereocenters, the AB-ring fragment **5** was prepared from **16** through five-step functional group manipulations (Scheme 3). After the three *cis*-hydroxy groups were protected as the orthoester, the remaining tertiary hydroxy group of **17** was regioselectively dehydrated using $POCl_3$ to produce **18**. Ozonolysis of tetrasubstituted olefin **18** gave rise to C7-ketone **19**, the X-ray crystallographic analysis of which confirmed β-orientations of the three hydroxy and C19-hydroxy methyl groups. Finally, $Pd(OCOCF_3)_2$-promoted dehydrogenation,[23] followed by TBAF-treatment, transformed **19** into the requisite **5**.

We have thus reached a critical stage in the total synthesis, *i.e.*, unification of the two fragments (**5**, *meso*-**B**) and stereoselective construction of the tetracyclic system by a combination of intramolecular radical and aldol reactions (Scheme 4). Before the coupling, the vinyl ether of D-ring *meso*-**B** was converted to dibromide **E**. The C19-hydroxy group of AB-ring **5** selectively displaced the *O*-activated C11′-bromo group of **E** in the presence of an acid scavenger $PhNMe_2$, leading to acetal **4** as a diastereomixture. The remaining C11-bromo group of **4** was in turn utilized as a radical donor by treatment with Et_3B/O_2[24] and



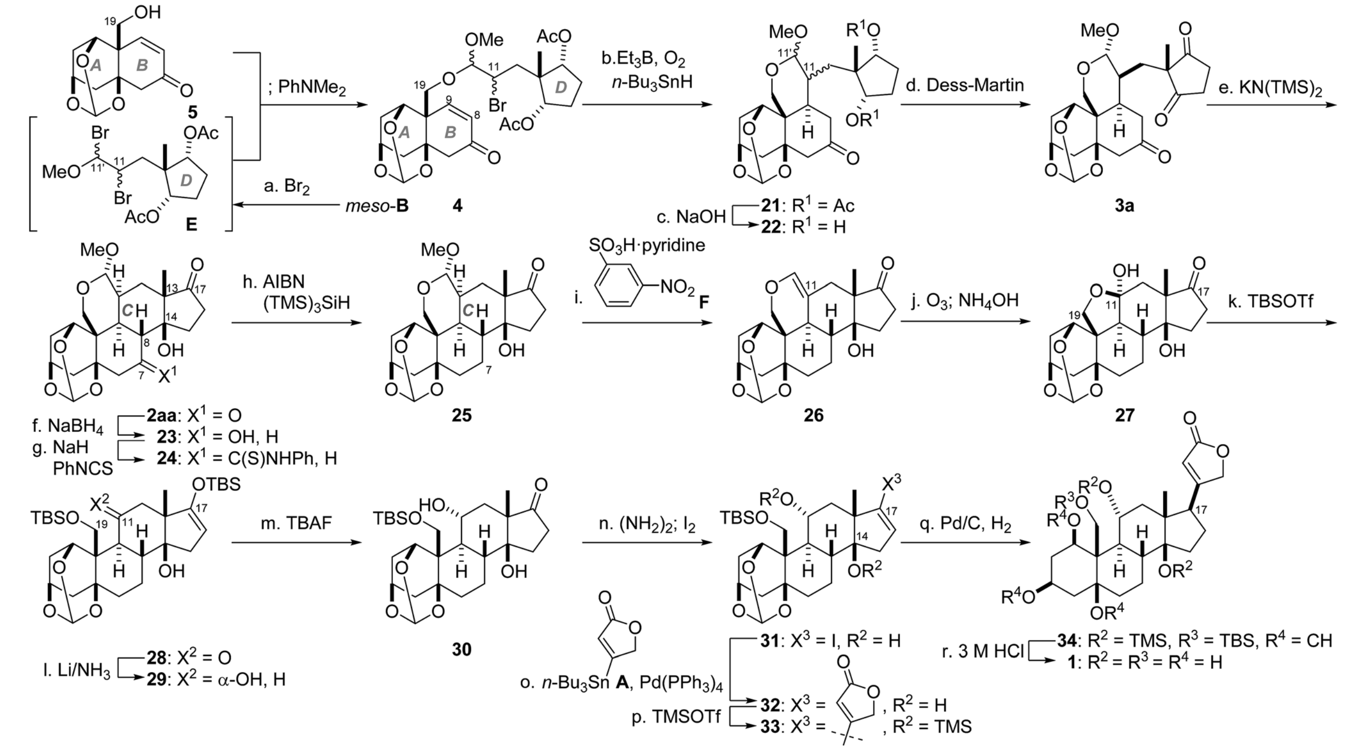
Scheme 3 Stereoselective synthesis of AB-ring **5**. *Reagents and conditions*: (a) toluene, 110 °C; 1.2 M aqueous HCl, THF, 67%; (b) $LiAlH_4$, Et_2O, −78 °C, 80%; (c) MnO_2, CH_2Cl_2, 89%; (d) TBSOTf, Et_3N, CH_2Cl_2, 0 °C; (e) $Pd(OAc)_2$, CH_3CN, 0 °C, 81% (2 steps); (f) **D**, *t*-BuOMe, Et_2O, −100 to −40 °C, 68% for **12** (dr = 3 : 1); (g) *m*-chloroperbenzoic acid (*m*-CPBA), $NaHCO_3$, CH_2Cl_2, 0 °C, 82%; (h) Dess–Martin reagent, $NaHCO_3$, CH_2Cl_2, 0 °C, 100%; (i) Al/Hg, $NaHCO_3$, THF, EtOH, H_2O, 0 °C; (j) diisobutylaluminium hydride (DIBAL-H), CH_2Cl_2, −40 °C; (k) *p*-tolSO_3H·pyridine, $HC(OMe)_3$, DMF, 0 °C; (l) $POCl_3$, pyridine, 0 °C; (m) O_3, CH_2Cl_2, −78 °C; Me_2S, 22% (5 steps); (n) $Pd(OCOCF_3)_2$, NaOAc, DMSO, 50 °C, 91%; (o) tetra-*n*-butylammonium fluoride (TBAF), AcOH, THF, 50 °C, 91%.

n-Bu_3SnH. The acetal tether of **4** effectively constrained the generated radical to add from the β-face of the C9-olefin to provide **21** (C11,11′-diastereomixture).[25] Saponification of the two acetates of **21** and subsequent Dess–Martin oxidation of **22** furnished the diastereomerically pure triketone **3a** after chromatographic purification (26% yield from **5**). As expected from the computational simulation and the model experiments in Scheme 2, the acetal-tethered **3a** was selectively converted into the desired isomer **2aa**. Specifically, treatment of **3a** with $KN(TMS)_2$ (30 mol%) in refluxing THF delivered desired **2aa** (65%) along with its minor diastereomer **2ab** (8%). Of note, this mild five-step sequence realized introduction of four new stereocenters (C8, 9, 13 and 14) without affecting the pre-existing oxygen functionalities.

Having constructed the properly substituted steroid, ouabagenin (**1**) was synthesized from **2aa** through adjustments of the C7,11-functional groups, attachment of the C17-butenolide and global deprotection. First, the C7-oxygen functionality was removed. Chemoselective $NaBH_4$ reduction at C7 of diketone **2aa** afforded alcohol **23**, which was derivatized into thiocarbamate **24** by means of thioisocyanate and NaH.[26,27] Reductive cleavage of the C7-thiocarbamate of **24** was realized by mixing with AIBN and $(TMS)_3SiH$ in refluxing benzene, providing **25**. Next, the α-oriented C11-hydroxy group was constructed from the C11-branched carbon linker, which served as the stereocontrolling element. Before doing so, the acetal of **25** was converted to the vinyl ether of **26** by acid-promoted elimination of MeOH.[28] Oxidative scission of the resultant C11-olefin of **26** with ozone, reductive workup and the basic deformylation at C19-OH gave hemiacetal **27**. TBSOTf and Et_3N then introduced TBS groups at both C19- and C17-oxygen atoms of **27**, liberating the C11-ketone of **28**. Subjection of **28** to Birch reduction conditions resulted in formation of **29** with the thermodynamically favorable equatorial C11-OH group.

The β-oriented C17-butenolide was incorporated through the Stille coupling reaction[29] and stereoselective hydrogenation (Scheme 4). Treatment of bis-TBS ether **29** with TBAF at −78 °C resulted in formation of C17-ketone **30**, which was in turn transformed to vinyl iodide **31** *via* the hydrazone intermediate.[30] The Stille coupling between **31** and **A** proceeded in the presence of $Pd(PPh_3)_4$ and CuCl in DMSO,[31] leading to **32** bearing the entire carbon structure of **1**. To achieve hydrogenation from the concave α-face of the 'U'-shape skeleton, the C14-hydroxy group of **32** was capped with the bulky TMS-ether to generate **33**. Presumably because the C14-OTMS blocked the approach of reagents from the β-face, Pd/C-catalyzed hydrogenation of **33** occurred selectively from the α-face to yield **34** as the major product. Finally, global deprotection of **34** with 3 M HCl in MeOH removed the two TMS, one TBS and one methine groups, giving rise to ouabagenin (**1**). The analytical data of synthetic **1** including the optical rotation, IR, ^1H-, ^{13}C-NMR and HRMS were identical with those of authentic **1**.

In conclusion, we achieved the convergent total synthesis of ouabagenin (**1**) using highly functionalized AB-ring **5** together with the simple achiral D-ring *meso*-**B** and butenolide **A** (33 steps from (*R*)-perillaldehyde **6**). After preinstalling the four stereocenters of **5**, introduction of the six remaining stereocenters and construction of the entire pentacyclic structure of **1** required only 18 steps, demonstrating the efficiency of the strategy. The key transformations that enabled the convergent synthesis include: (i) the mild acetal formation between AB-ring **5** and dibromide **E**; (ii) the tether-guided 6-exo radical cyclization of **4**; (iii) the stereoselective aldol reaction of triketone **3a** that was judiciously designed based on *in silico* and model



Scheme 4 Total synthesis of ouabagenin (**1**). *Reagents and conditions*: (a) *meso*-**B** (2.5 equiv.), Br_2, CH_2Cl_2, −78 °C; **5** (1.0 equiv.), $PhNMe_2$; (b) Et_3B, *n*-Bu_3SnH, O_2, toluene; (c) NaOH, MeOH, H_2O; (d) Dess–Martin reagent, $NaHCO_3$, CH_2Cl_2, 26% for **3a** (4 steps from **5**); (e) $KN(TMS)_2$ (30 mol%), THF, reflux, 65% for **2aa**, 8% for **2ab**; (f) $NaBH_4$, THF; (g) NaH, H_2O, PhNCS, THF; (h) AIBN, $(TMS)_3SiH$, benzene, reflux, 39% (3 steps); (i) **F**, toluene, reflux, 81%; (j) O_3, MeOH, −78 °C; Me_2S; NH_4OH; (k) TBSOTf, Et_3N, CH_3CN, −35 to 0 °C, 68% (2 steps); (l) Li, NH_3, THF, −78 °C, 96%; (m) TBAF, THF, −78 °C, 99%; (n) $(NH_2)_2$, Et_3N, EtOH, 50 °C; I_2, Et_3N, THF, 89%; (o) **A** (3.0 equiv.), $Pd(PPh_3)_4$, LiCl, CuCl, DMSO, 60 °C; (p) TMSOTf, 2,6-lutidine, CH_2Cl_2; SiO_2, 58% (2 steps); (q) H_2, Pd/C, EtOAc; (r) 3 M aqueous HCl, MeOH, 56% (2 steps).

experiments; (iv) installation of the C17-butenolide by the Stille coupling using **A**; (v) the stereoselective hydrogenation of C17-double bond; and (vi) the single-step global deprotection. Because of its flexibility and robustness, the present route would be applicable for the synthesis of a variety of bioactive cardenolides, and synthetic and SAR studies of such molecules will be our next focus.

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