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Cite this: *Chem. Sci.*, 2015, 6, 3383

Received 20th January 2015

Accepted 28th March 2015

DOI: 10.1039/c5sc00212e

www.rsc.org/chemicalscience

A convergent total synthesis of ouabagenin†

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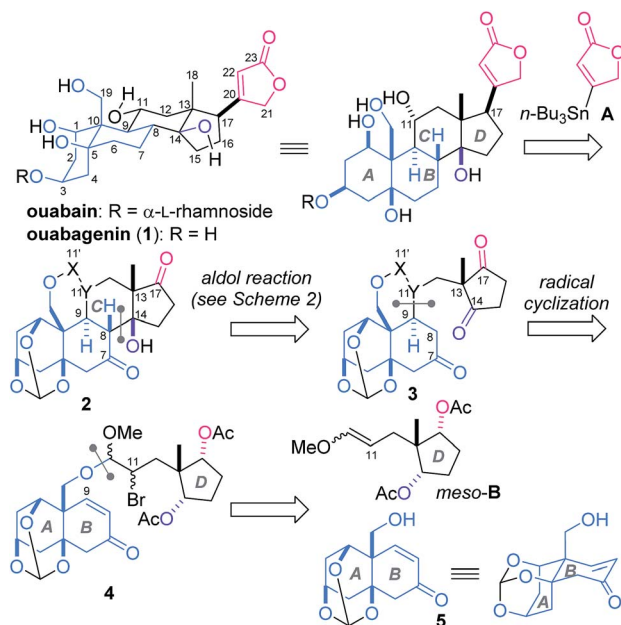
A convergent total synthesis of ouabagenin, an aglycon of cardenolide glycoside ouabain, was achieved by assembly of the AB-ring, D-ring and butenolide moieties. The multiply oxygenated *cis*-decalin structure of the AB-ring was constructed from (*R*)-perillaldehyde through the Diels–Alder reaction and 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

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



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

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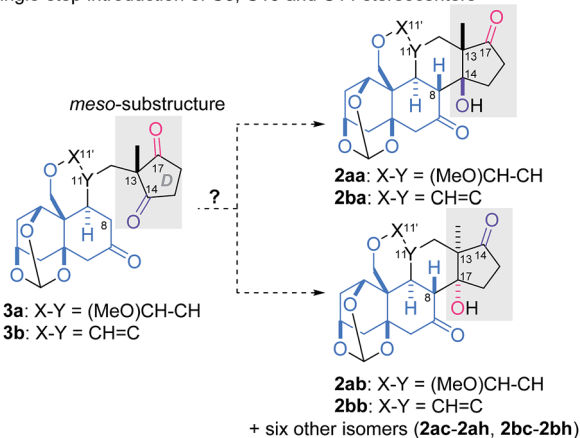
† Electronic supplementary information (ESI) available: Characterization data for all new compounds, experimental procedures. CCDC 1027184 and 1027185. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5sc00212e



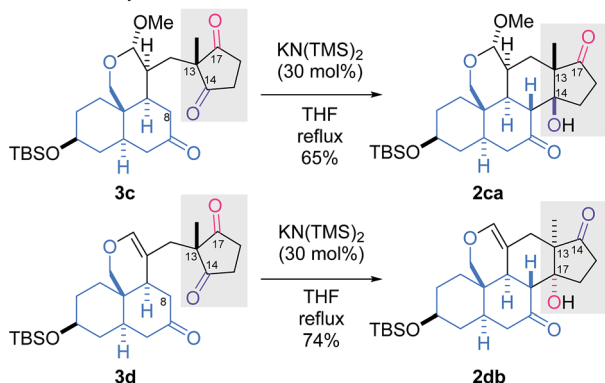
remaining six centers were planned to be installed en route to **1**. Most importantly, the stereochemistry of the four angular positions (C8, 9, 13, 14) was to be controlled by two intramolecular reactions. After tethering **5** and *meso*-**B** through the acetal linkage, 6-exo radical cyclization 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).

A. Single-step introduction of C8, C13 and C14 stereocenters



B. Model study of the aldol reaction



Scheme 2 Design of the substrates of Aldol reaction.

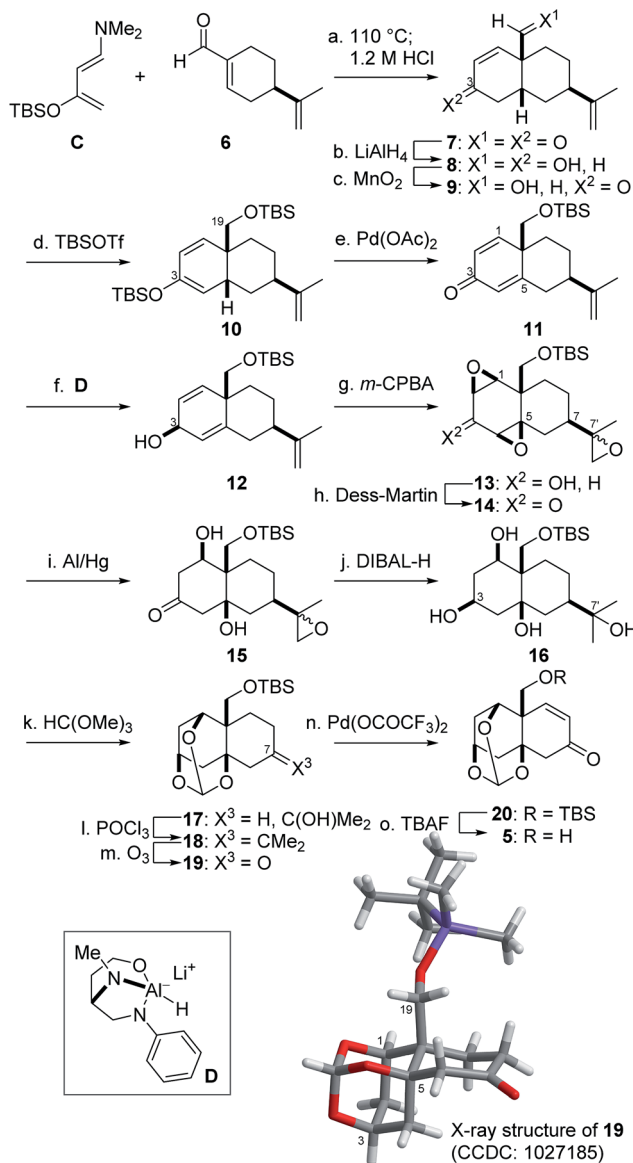
To experimentally examine the role of the linker (X–Y), the synthetically more accessible models **3c** and **3d** were prepared and subjected to the aldol reactions (Scheme 2B).¹³ Despite their abbreviated structures, the *trans*-decalin rings of **3c** and **3d** were assumed to mimic the rigid orthoester-protected 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 LiAlH₄ to produce diol **8**, the allylic alcohol of which was chemoselectively oxidized with MnO₂ to provide ketone **9**. Treatment of **9** with TBSOTf and Et₃N then introduced the two TBS groups at the C3-enol and C19-hydroxy groups, resulting in **10**. Pd(OAc)₂-mediated oxidation¹⁷ 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 oxidation²¹ 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 POCl₃ 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(OCOCF₃)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 PhNMe₂, 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 Et₃B/O₂²⁴ and





Scheme 3 Stereoselective synthesis of AB-ring 5. *Reagents and conditions:* (a) toluene, 110 °C; 1.2 M aqueous HCl, THF, 67%; (b) LiAlH₄, Et₂O, -78 °C, 80%; (c) MnO₂, CH₂Cl₂, 89%; (d) TBSOTf, Et₃N, CH₂Cl₂, 0 °C; (e) Pd(OAc)₂, CH₃CN, 0 °C, 81% (2 steps); (f) D, *t*-BuOMe, Et₂O, -100 to -40 °C, 68% for 12 (dr = 3 : 1); (g) *m*-chloroperbenzoic acid (*m*-CPBA), NaHCO₃, CH₂Cl₂, 0 °C, 82%; (h) Dess–Martin reagent, NaHCO₃, CH₂Cl₂, 0 °C, 100%; (i) Al/Hg, NaHCO₃, THF, EtOH, H₂O, 0 °C; (j) diisobutylaluminium hydride (DIBAL-H), CH₂Cl₂, -40 °C; (k) *p*-tolSO₃H·pyridine, HC(OMe)₃, DMF, 0 °C; (l) POCl₃, pyridine, 0 °C; (m) O₃, CH₂Cl₂, -78 °C; Me₂S, 22% (5 steps); (n) Pd(OCOCF₃)₂, NaOAc, DMSO, 50 °C, 91%; (o) tetra-*n*-butylammonium fluoride (TBAF), AcOH, THF, 50 °C, 91%.

n-Bu₃SnH. 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

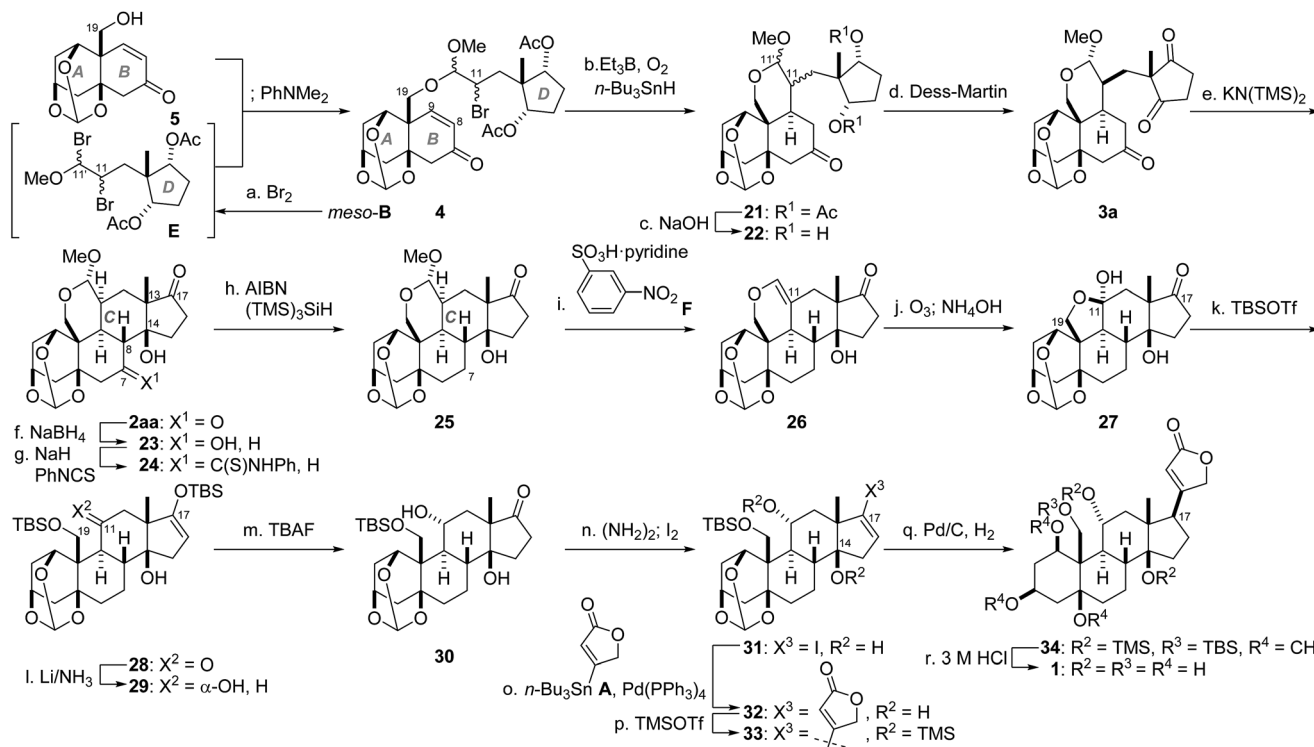
Scheme 2, the acetal-tethered 3a was selectively converted into the desired isomer 2aa. Specifically, treatment of 3a with KN(TMS)₂ (30 mol%) in refluxing THF delivered desired 2aa (65%) along with its minor diastereomer 2ab (8%). Of note, this mild five-step sequence realized introduction of four new 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 NaBH₄ 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 with ozone, reductive workup and the basic deformylation at C19-OH gave hemiacetal 27. TBSOTf and Et₃N 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 reaction²⁹ 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(PPh₃)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-, ¹³C-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.), Br₂, CH₂Cl₂, -78 °C; **5** (1.0 equiv.), PhNMe₂; (b) Et₃B, *n*-Bu₃SnH, O₂, toluene; (c) NaOH, MeOH, H₂O; (d) Dess–Martin reagent, NaHCO₃, CH₂Cl₂, 26% for **3a** (4 steps from **5**); (e) KN(TMS)₂ (30 mol%), THF, reflux, 65% for **2aa**, 8% for **2ab**; (f) NaBH₄, THF; (g) NaH, H₂O, PhNCS, THF; (h) AIBN, (TMS)₃SiH, benzene, reflux, 39% (3 steps); (i) F, toluene, reflux, 81%; (j) O₃, MeOH, -78 °C; Me₂S; NH₄OH; (k) TBSOTf, Et₃N, CH₃CN, -35 to 0 °C, 68% (2 steps); (l) Li, NH₃, THF, -78 °C, 96%; (m) TBAF, THF, -78 °C, 99%; (n) (NH₂)₂, Et₃N, EtOH, 50 °C; I₂, Et₃N, THF, 89%; (o) **A** (3.0 equiv.), Pd(PPh₃)₄, LiCl, CuCl, DMSO, 60 °C; (p) TMSOTf, 2,6-lutidine, CH₂Cl₂; SiO₂, 58% (2 steps); (q) H₂, 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.

Acknowledgements

This research was financially supported by the Funding Program for a Grant-in-Aid for Scientific Research (A) (JSPS) to M.I., and (C) (JSPS) and on Innovative Areas (MEXT) to D.U. A fellowship to K.M. and S.K. from JSPS is gratefully acknowledged. We thank Naoto Aoki for preparation of **2db**, and Dr Kimiko Hasegawa (Rigaku Corporation) for X-ray crystallographic analyses.

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