dropping as a result of the increased total spin as manifested by the sharper line shape in $M(B)$ (Fig. 4C). As the size of the magnet increases, similar behavior is seen in $q(I_t)$, but the overall value of q needed to reverse the larger magnet increases (Fig. 2, A and B). The general shape of $q(T)$ (Fig. 3B) persists for larger magnets, proving that the underlying mechanisms that govern the dynamics remain the same. Whereas D and E change as the size of the magnet increases, thus affecting $\tau^*(I_t,V_s)$, the strong increase in q needed to switch the magnet as the magnet gets larger is most likely a consequence of the increased spin of the magnet. Increasing the spin results in an increased number of sequential transitions needed to reverse the magnetization, requiring a higher total charge to reverse the magnetic state.

Although the relaxation of the magnets studied here is far from purely quantum, namely the quantum phase is destroyed, it is surprising that, for such a strongly hybridized spin coupled to an electron bath, quantum effects are indeed necessary to fully describe the dynamics of the system. The strength of the STT studied here is determined solely by the total spin polarization of the tip independent of the total current (*24*). This can be seen in the nearly constant asymmetry in Fig. 2, A and B, and fig. S4 regardless of the mean switching frequency ν*, illustrating the quantum nature of STT in atomic-scale magnets (*16*). Our work brings to light fundamental processes of interest for future magnetic memory devices that are scaled to atomic dimensions.

References and Notes

1. J. Åkerman, *Science* **308**, 508 (2005).
2. M. N. Baibich *et al.*, *Phys. Rev. Lett.* **61**, 2472 (1988).
3. B. Dieny *et al.*, *Phys. Rev. B* **43**, 1297 (1991).
4. J. Slonczewski, *J. Magn. Magn. Mater.* **159**, L1 (1996).
5. L. Berger, *Phys. Rev. B* **54**, 9353 (1996).
6. D. Ralph, M. Stiles, *J. Magn. Magn. Mater.* **320**, 1190 (2008).
7. A. Brataas, A. D. Kent, H. Ohno, *Nat. Mater.* **11**, 372 (2012).
8. M. Tsoi *et al.*, *Phys. Rev. Lett.* **80**, 4281 (1998).
9. E. B. Myers, D. C. Ralph, J. A. Katine, R. N. Louie, R. A. Buhrman, *Science* **285**, 867 (1999).
10. S. S. P. Parkin, M. Hayashi, L. Thomas, *Science* **320**, 190 (2008).
11. M. Tsoi *et al.*, *Nature* **406**, 46 (2000).
12. S. I. Kiselev *et al.*, *Nature* **425**, 380 (2003).
13. F. Meier, L. Zhou, J. Wiebe, R. Wiesendanger, *Science* **320**, 82 (2008).
14. W. Wernsdorfer, R. Sessoli, *Science* **284**, 133 (1999).
15. D. Gatteschi, R. Sessoli, *Molecular Nanomagnets* (Oxford Univ. Press, Oxford, ed. 1, 2006).
16. F. Delgado, J. J. Palacios, J. Fernández-Rossier, *Phys. Rev. Lett.* **104**, 026601 (2010).
17. S. Loth *et al.*, *Nat. Phys.* **6**, 340 (2010).
18. M. Misiorny, J. Barnaś, *Phys. Rev. B* **76**, 054448 (2007).
19. S. Loth, S. Baumann, C. P. Lutz, D. M. Eigler, A. J. Heinrich, *Science* **335**, 196 (2012).
20. A. A. Khajetoorians *et al.*, *Phys. Rev. Lett.* **106**, 037205 (2011).
21. T. Schuh *et al.*, *Phys. Rev. B* **84**, 104401 (2011).
22. D. L. Mills, P. Lederer, *Phys. Rev.* **160**, 590 (1967).
23. D. M. Eigler, E. K. Schweizer, *Nature* **344**, 524 (1990).
24. Materials and methods are available as supplementary material on *Science* Online.
25. A. A. Khajetoorians *et al.*, *Nat. Phys.* **8**, 497 (2012).
26. A. Bergman, L. Nordström, A. Burlamaqui Klautau, S. Frota-Pessôa, O. Eriksson, *Phys. Rev. B* **75**, 224425 (2007).
27. S. Krause, L. Berbil-Bautista, G. Herzog, M. Bode, R. Wiesendanger, *Science* **317**, 1537 (2007).
28. C. F. Hirjibehedin, C. P. Lutz, A. J. Heinrich, *Science* **312**, 1021 (2006); 10.1126/science.1125398.
29. J. Fransson, *Nano Lett.* **9**, 2414 (2009).
30. N. Lorente, J.-P. Gauyacq, *Phys. Rev. Lett.* **103**, 176601 (2009).
31. H. Gawronski, M. Mehlhorn, K. Morgenstern, *Science* **319**, 930 (2008).
32. T. Gilbert, *IEEE Trans. Magn.* **40**, 3443 (2004).

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Supplementary Materials

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Materials and Methods
Supplementary Text
Figs. S1 to S4
References (*33*–*48*)

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Strategic Redox Relay Enables A Scalable Synthesis of Ouabagenin, A Bioactive Cardenolide

Hans Renata, Qianghui Zhou, Phil S. Baran*

Here, we report on a scalable route to the polyhydroxylated steroid ouabagenin with an unusual take on the age-old practice of steroid semisynthesis. The incorporation of both redox and stereochemical relays during the design of this synthesis resulted in efficient access to more than 500 milligrams of a key precursor toward ouabagenin—and ultimately ouabagenin itself—and the discovery of innovative methods for carbon-hydrogen (C-H) and carbon-carbon activation and carbon-oxygen bond homolysis. Given the medicinal relevance of the cardenolides in the treatment of congestive heart failure, a variety of ouabagenin analogs could potentially be generated from the key intermediate as a means of addressing the narrow therapeutic index of these molecules. This synthesis also showcases an approach to bypass the historically challenging problem of selective C-H oxidation of saturated carbon centers in a controlled fashion.

In the realm of terpene synthesis, nature has evolved a highly efficient biosynthetic system to achieve chemo- and stereoselective oxidations far beyond the capabilities of chemical synthesis in the laboratory. For example, the complex steroid ouabagenin is thought to have arisen from progesterone (Fig. 1A) through a series of direct, chemoselective oxidations employing a multitude of hydroxylase enzymes (*1*). A step-by-step emulation of this oxidation sequence is difficult, if not impossible, to execute in a laboratory setting. As a way to circumvent this direct oxidation problem, a plethora of directed oxidation methods have been invented (*2*), whereby a template is typically appended to effect site-selective oxidation(s) on a molecular framework. Historically, another approach, which relies on the indirect use of preexisting functional groups of the framework in the absence of a directing template, has also been widely employed, as evidenced by the wealth of synthesis literature on terpene functionalizations (*3*, *4*). Use of this approach has enabled semisyntheses of highly complex steroids such as digitoxin (*5*), batrachotoxin (*6*), dihydroconessine (*7*), cephalostatin 1 (*8*), cortistatin A (*9*), and withanolide A (*10*) and has laid a foundation for pharmaceutical research on commercial semisynthetic steroid medicines such as finasteride, dexamethasone, and progestin. Despite these achievements, the scalable synthesis of polyhydroxylated steroids (more than five hydroxyl moieties on the tetracyclic skeleton) (Fig. 1B) is unknown. Here, we report the accomplishment of such a feat using a quasibiomimetic oxidation approach, which relies on the strategic interplay of two relay elements: (i) redox relay, defined as rapid (one or two steps) transfer of redox information from one site to another within a framework, and (ii) oxidative stereochemical relay, defined as transfer of stereochemical information during an oxidative process. It is the interplay of both strategies, rather than their isolated use, that distinguishes this synthesis from conventional strategies.

Ouabagenin (**1**) was specifically chosen as a target molecule to showcase the application of this quasibiomimetic oxidation strategy because of its highly oxidized molecular framework and its biological relevance as a positive inotrope (*11*).

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Ouabagenin belongs to a unique class of steroids, known as cardenolides, possessing both cis A/B and C/D ring fusions with an angular hydroxyl moiety at C14, as well as a β-oriented butenolide substituent at C17. The high oxidation level of its framework poses a formidable challenge for synthesis efforts and, in addition, the predominantly β orientation of its polyhydroxylation pattern renders ouabagenin an able ligand to inorganic species (*12*), including borosilicate glassware. Its parent glycoside, ouabain, along with digoxin and digitoxin, is used as a treatment for congestive heart failure, a progressive condition that currently affects approximately two million people in the United States alone (*13*). The use of cardiotonic steroids, however, is complicated by an extremely narrow therapeutic index, and patients are often treated with 60% of the toxic dose. Although structure-activity relationship studies have been conducted on cardenolides and related bufadienolides (*14*), they have been limited to hydroxylated analogs, and studies on other heterocyclic analogs are relatively rare. Thus, a de novo synthesis that would allow versatile topological diversification could lead to the development of further analogs potentially possessing a wider therapeutic window as safer alternatives (*15*). A previous synthesis of ouabagenin by Deslongchamps and colleagues, although an elegant accomplishment, proceeded in 41 steps from Hajos-Parrish ketone in 0.21% overall yield, producing 7 mg of their most advanced intermediate, which was intercepted by a relay synthesis from degradation of authentic ouabain to arrive at ouabagenin in 8 steps (*16*). In addition, several synthetic studies on this molecule have been disclosed (*17*).

In our synthesis planning (Fig. 1C), we envisioned that the butenolide moiety would be appended late in the synthesis, revealing the ouabagenin ketonic core, so-called ouabageninone (**2**), in a retrosynthetic sense. Three relay events, systematically applied during the planning stage, formed the basis of our approach. The first required installation of the tertiary alcohol at C14 on pentaol **3** through relay of the redox information coded in the C17 ketone. Oxidative stereochemical relay—another modality of this strategy—would leverage the primary alcohol at C19 to correctly install the requisite oxidation state at the C1 and C5 positions. Last, disconnection of the hydroxyl group at C19 inspired the invention of a redox relay from the C11 ketone functionality of **5**. The requisite hydroxyl moieties at C3 and C11 would be generated from stereocontrolled reductions of the respective carbonyl groups. In light of the affinity of the fully functionalized A ring for inorganic species and common laboratory glassware, strategic protection would be applied on the more advanced intermediates for their ease of handling. Given the need for a scalable and economically viable route to the cardenolides and derivatives thereof, cortisone acetate (**6**, ~US$1/gram, from OChem Incorporated) was chosen as an ideal starting material. The realization of this strategy enabled the scalable synthesis of ouabagenin, where all steps up to step M (Fig. 2) have been conducted on a gram scale.

Cortisone acetate was converted to adrenosterone **5** (also commercially available, but more expensive) employing a modified protocol (see supplementary materials) that proceeded in 86% yield (Fig. 2). After ketalization and recrystallization, the first redox-relay event of the route was realized in the Norrish type II photochemical functionalization of the angular C19 methyl group by the C11 ketone moiety (*18*) because we were unable to reproduce a porphyrin-catalyzed, direct C19 methyl hydroxylation report (*19*). Initial experimentation revealed that although desired cyclobutanol **7** could be obtained by conventional solution photochemistry, the reaction proceeded in only modest yield (see supplementary materials) and was plagued by competitive formation

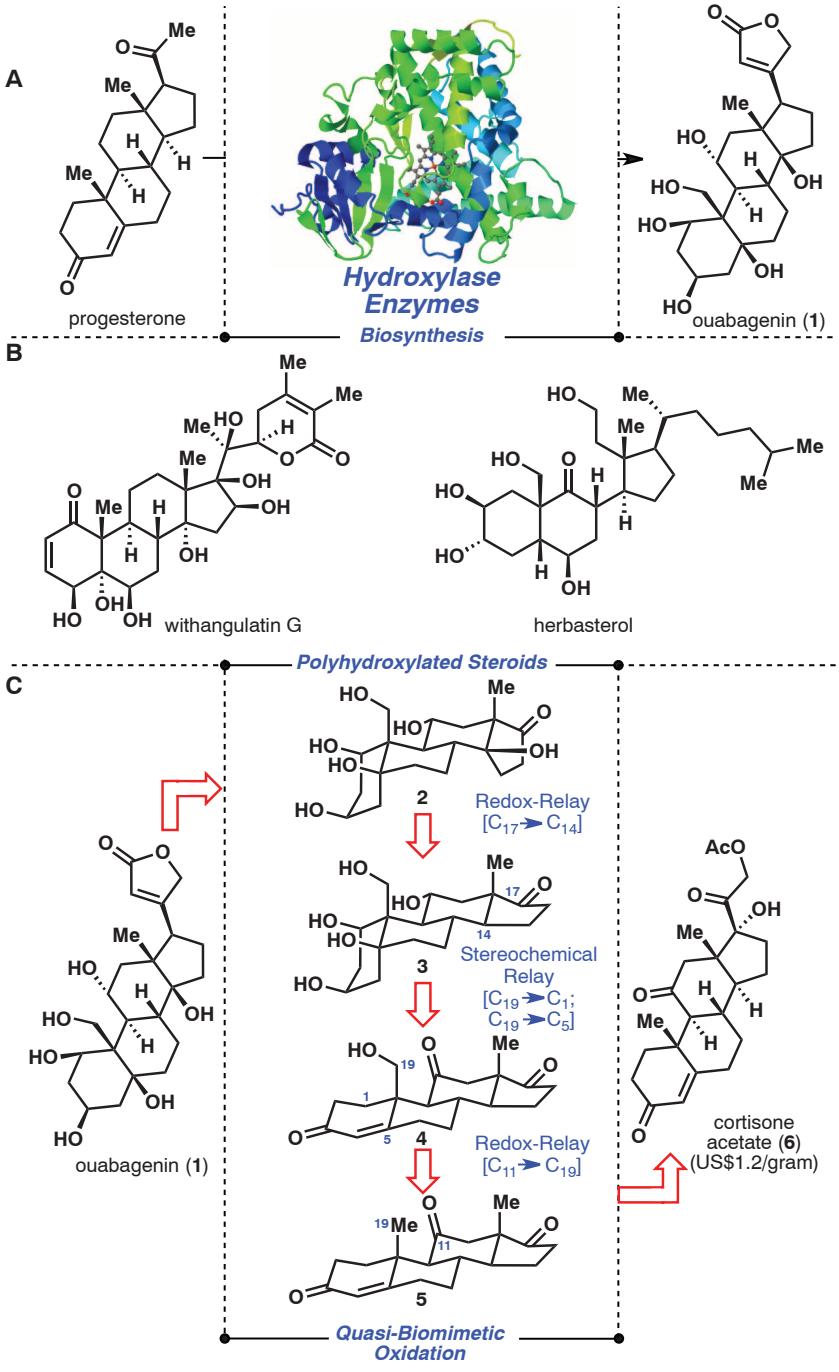


Fig. 1. (**A**) Biosynthesis of the highly complex steroid ouabagenin. Structure of a typical hydroxylase enzyme is shown. Image from the Research Collaboratory for Structural Bioinformatics Protein Data Base (PDB) (www.pdb.org) of PDB ID 1FAH (*41*). (**B**) Selected examples of polyhydroxylated steroids. (**C**) Retrosynthetic analysis of ouabagenin.

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of side products, most notably from Norrish type I cleavage of the C9-C11 bond of the steroidal framework. We therefore explored solid-state irradiation of ketalized **5** in aqueous suspension—drawing inspiration from Garcia-Garibay's work on synthesis using solid-state Norrish type I photochemistry (*20*)—which, to our delight, not only improved the yield for the cyclobutanol formation but also led to notable suppression of side products. This improvement in chemoselectivity comes with a trade-off in the rate of the reaction (3 to 5 days to ~90% conversion, 2.5-g scale), presumably due to the limited exposure of solid surface area in a typical photoreaction vessel. The use of a flow reactor should improve the reaction efficiency and allow this reaction to be conducted on an even larger scale because continuous operation will allow more uniform exposure of solid surface area and closer positioning to the light source (*21*).

Although the crystal structure analysis of **7** revealed weaker bond strength of the C11-C19 bond relative to the C9-C11 bond, initial attempts to effect oxidative fragmentation (*18*, *22*) of the C11-C19 bond were met with failure; for example, use of (diacetoxyiodo)benzene resulted in the undesired fragmentation of the C9-C11 bond. Eventually, iodide **8** could be obtained in excellent yield by the use of Barluenga's reagent (*23*), but the cost of the reagent proved to be a substantial drawback for large-scale operations. A more economical alternative was finally realized by using N-iodosuccinimide as the oxidant (*24*). This transformation is likely to proceed via the intermediacy of a transient hypoiodite species, which undergoes a chemoselective homolysis of the C11-C19 bond, followed by recombination with an iodine radical. Selective deketalization of C3 and hydrolysis of the C19 iodide moiety furnished enone alcohol **9**, which was primed for the next series of relay events, where the C19 hydroxyl moiety would serve to facilitate the introduction of additional hydroxyl moieties on C1 and C5. In addition, we surmised that the angular disposition of the C19 hydroxyl moiety would also translate to a diastereoselective stereochemical relay to the β face of the A ring. Success was eventually realized by epoxidation of the enone moiety that—in contrast to epoxidation literature on simpler C19 methyl substrates (*25*)—proceeded with complete facial selectivity, likely through the formation of a hydrogen-bonding network under the protic conditions of the reaction. Dehydrogenation of the C1-C2 bond of the resulting epoxide with selenium dioxide, followed by another iteration of a directed epoxidation event, provided diepoxide **11** in good yield. Facial selectivity of the two epoxidation events was confirmed by x-ray analysis after deketalization.

Reductive opening of diepoxide **11** proved to be the most difficult transformation to secure on scale. A gamut of conditions was surveyed (*26*), only to give a mixture of A ring enones as products. Triol **12** was only accessible via treatment with in situ generated aluminum amalgam. Preliminary trials of the use of this reagent in a mixture of organic solvent and water were beset by unsatisfactory conversion and observation of partial reduction of the epoxides (only one epoxide was cleaved, and the other remained intact). After extensive optimization, we found that

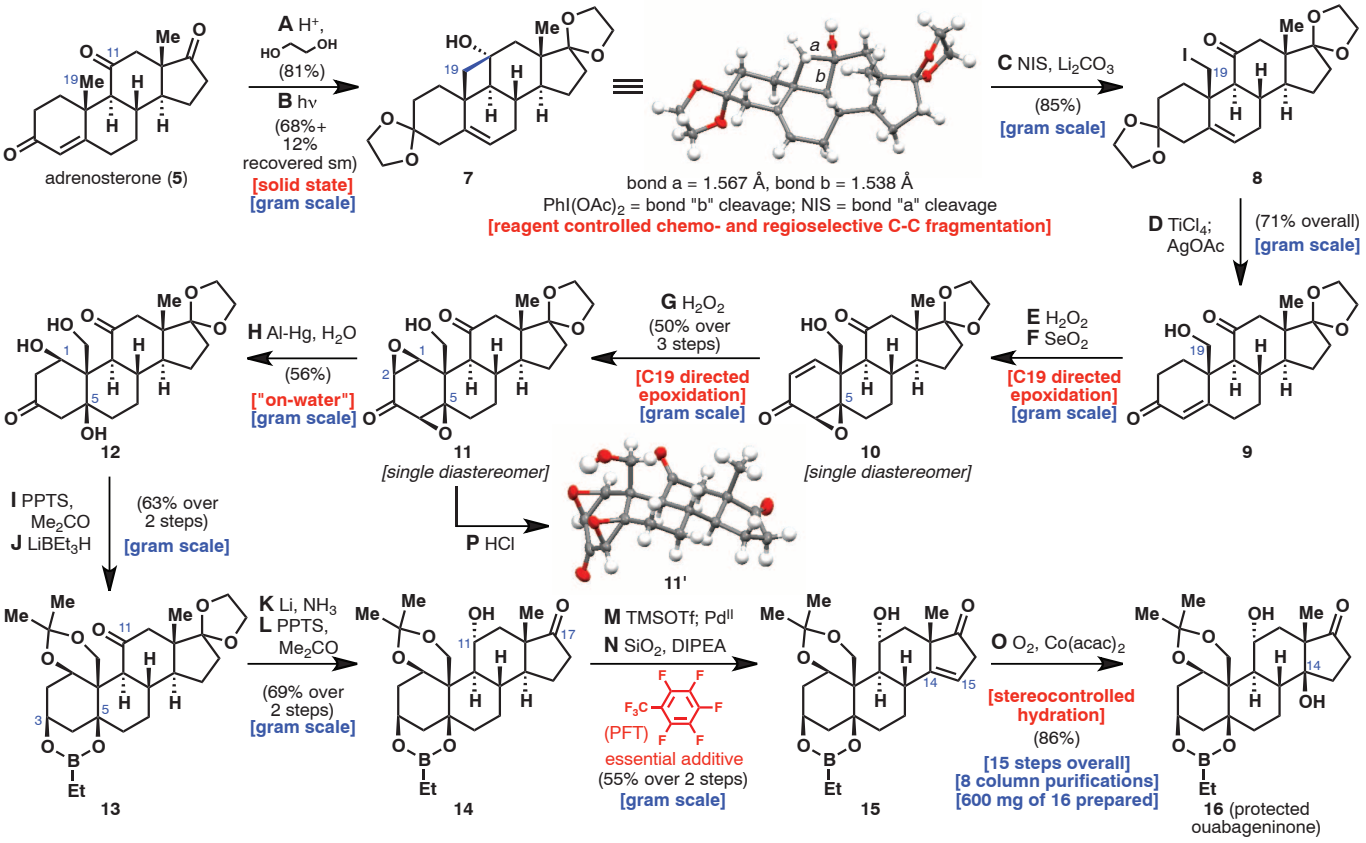


Fig. 2. Construction of the ouabagenin core. Reagents and conditions: (**A**) *p*-TsOH [0.1 equivalent (equiv.)], ethylene glycol (30 equiv.), $PhCH_3$, 135°C, 6 hours, 81%. (**B**) hν, SDS solution, 120 hours, 68%. (**C**) hν, N-iodosuccinimide (3 equiv.), Li_2CO_3 (3.5 equiv.), MeOH, $PhCH_3$, 23°C, 20 min, 85%. (**D**) $TiCl_4$ (1 M in CH_2Cl_2, 1 equiv.), CH_2Cl_2, –10°C, 15 min; AgOAc (1.5 equiv.), tetrahydrofuran (THF), 50°C, 2 hours, 71% overall. (**E**) H_2O_2 [35 weight percent (wt %) in H_2O, 6 equiv.], 3 M NaOH (1 equiv.), MeOH, 0°C, 75 min. (**F**) SeO_2 (1.1 equiv.), PhCl, 90°C, 10 hours. (**G**) H_2O_2 (35 wt % in H_2O, 6 equiv.), 3 M NaOH (1 equiv.), MeOH, 0°C, 75 min, 50% (over three steps). (**H**) Al-Hg, saturated $NaHCO_3$, –5°C, 1 hour, 56%. (**I**) Pyridinium *p*-toluenesulfonate (0.2 equiv.), $CaSO_4$ (2.5 equiv.), Me_2CO, 23°C, 20 hours. (**J**) $LiBEt_3H$ (1 M in THF, 1.1 equiv.), THF, –78°C, 30 min, 63% (over two steps). (**K**) Li (60 equiv.), NH_3, THF, –78°C, 30 min. (**L**) Pyridinium *p*-toluenesulfonate (1.5 equiv.), Me_2CO, 70°C, 16 hours, 69% (over two steps). (**M**) TMSOTf (3 equiv.), Et_3N (4 equiv.), CH_2Cl_2, 0 to 23°C, 30 min; $Pd(OAc)_2$ (1.2 equiv.), MeCN, 23°C, 3 hours, then $FeCl_3$ (1 equiv.), 0°C, 10 min. (**N**) SiO_2, iPr_2EtN (55 equiv.), C_7F_8, 45 min, 55% (over two steps). (**O**) $Co(acac)_2$ (0.2 equiv.), $PhSiH_3$ (3 equiv.), O_2, dioxane, 23°C, 3 hours, 86%. (**P**) Concentrated (conc.) HCl (1 equiv.), CH_2Cl_2, 23°C, 1 hour, 87%.

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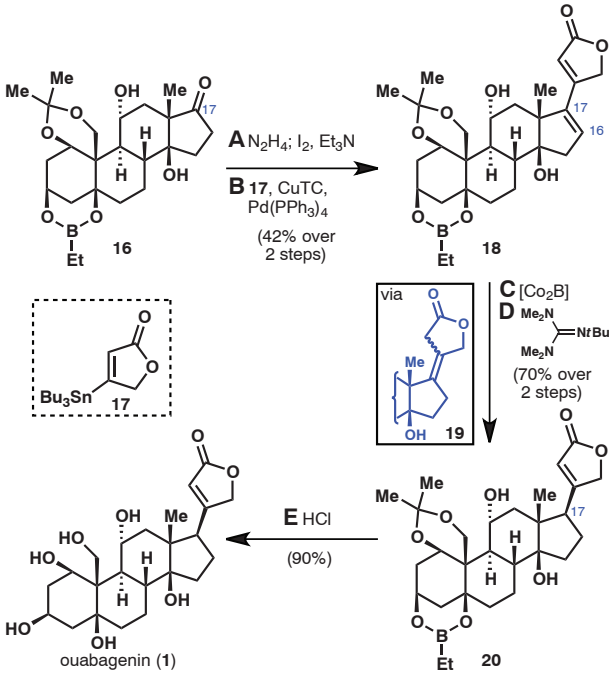
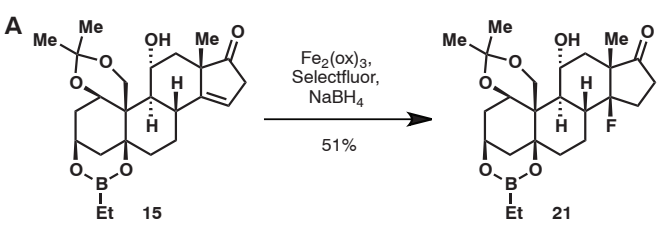


Fig. 3. Completing the synthesis of ouabagenin. Reagents and conditions: (**A**) N_2H_4 (10 equiv.), Et_3N (10 equiv.), 4:1 CH_2Cl_2:EtOH, 50°C, 5 hours; I_2 (3 equiv.), Et_3N (4 equiv.), THF, 10 min. (**B**) 17 (4 equiv.), $[Ph_2PO_2][NBu_4]$ (4 equiv.), $Pd(PPh_3)_4$ (0.15 equiv.), Cu(thiophene-2-carboxylate) (3 equiv.), *N*,*N*´-dimethylformamide (DMF), 23°C, 2 hours, 42% (over two steps). (**C**) $CoCl_2 \cdot 6H_2O$ (2.5 equiv.), $NaBH_4$ (5 equiv.), EtOH, 0 to 23°C, 20 min. (**D**) 2-tert-Butyl-1,1,3,3,-tetramethylguanidine (1.5 equiv.), C_6H_6, 100°C, 10 min, 70% (over two steps). (**E**) Conc. HCl (2 equiv.), MeOH, 23°C, 30 min, 90%.

the use of "on-water" (aqueous suspension) conditions (*27*) was critical to obtaining a satisfactory yield of triol **12**. Specifically, a saturated $NaHCO_3$ solution was found to be the optimal medium for this transformation (see supplementary materials). After acetonide formation, the ketone moiety on C3 was reduced with $LiBEt_3H$, which effected a concomitant formation of the ethyl boronic ester of the two hydroxyl moieties on C1 and C5, thereby bypassing the need for an additional protection step. The desired α configuration of the hydroxyl group on C11 could be accessed by employing a thermodynamic reduction (Li/NH_3). Last, mild deketalization of C17 set the stage for the final redox-relay event.

The C17 ketone moiety so revealed rendered the C15-C16 methylene subunits amenable to dehydrogenation to furnish the conjugated enone. Initial attempts at olefin isomerization on this enone (*28*), however, were hampered by low conversion and epimerization of the C14 stereocenter, which represented a dead end because this epimer could not be converted to **15**. Ultimately, we found that the use of fluorinated solvents, in particular perfluorotoluene, aided the conversion to **15**, while suppressing the epimerization of the



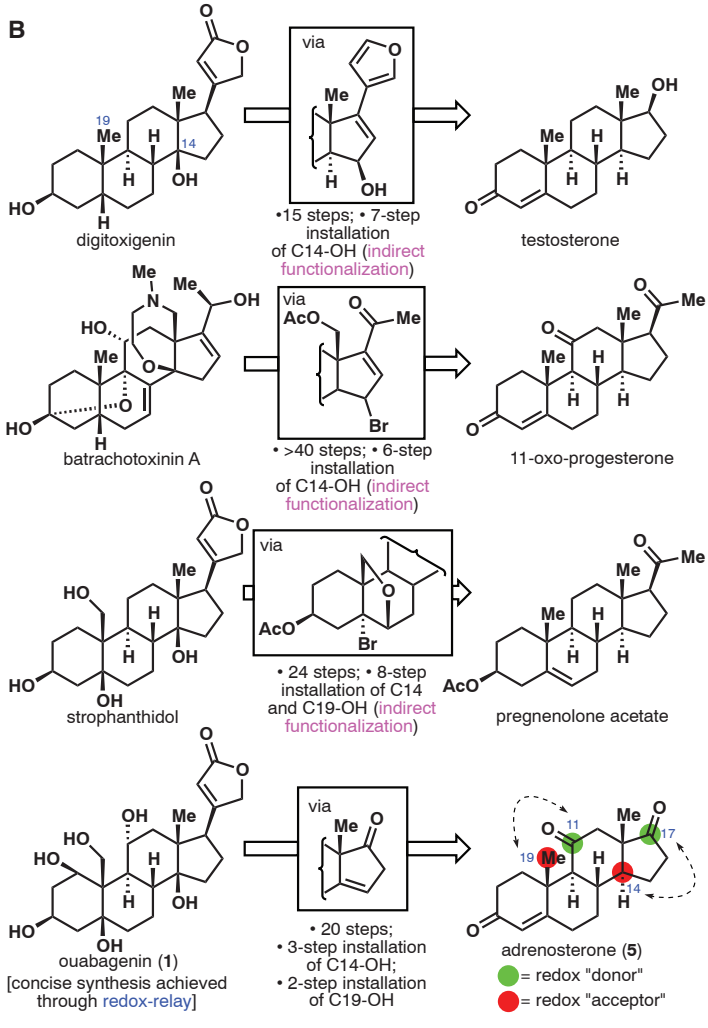


Fig. 4. (**A**) Late-stage functionalization of deconjugated enone. Reagents and conditions: $Fe_2(oxalate)_3$ (4 equiv.), Selectfluor (4 equiv.), $NaBH_4$ (6.4 equiv.), 3:4:2 MeCN:THF:H_2O, 0°C, 20 min, 51%. (**B**) Comparison to previous semisyntheses of related cardenolides.

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C14 center (see supplementary materials). Formation of π-π complexes has been suggested (*29*) in the observed catalyst activity enhancement of olefin metathesis in fluorinated aromatic solvents, and this phenomenon between perfluorotoluene and our enone system could also play a role in the rate enhancement of our isomerization reaction, although other effects—such as dielectric constant and silicon-fluorine interactions—cannot be ruled out. Mukaiyama hydration (*30*) of the resulting olefin, although straightforward, necessitated the use of dioxane as solvent to obtain a satisfactory diastereomeric ratio of hydration products (*dr* = 8:1, in favor of **16**). Success of this transformation marked the completion of strategically protected ouabageninone, the ketonic core of the target molecule that would enable not only the synthesis of ouabagenin but also the versatile access to analogs varied at C17, as well as the related bufadienolide family of natural products. As a testament to the scalability of this 15-step sequence, >500 mg of this molecule has been synthesized to date. Although it is definitely possible to convert the total amount of **16** that we have procured to date to more than 100 mg of the natural product, we are planning to use a substantial portion of this material as a branching point to access various analogs at C17 and profile their therapeutic indexes.

Attachment of the butenolide subunit (Fig. 3) was accomplished by first converting ketone **16** to the corresponding vinyl iodide using Barton's protocol (*31*) and then subjecting the product to a Stille cross-coupling with known stannane **17** (*32*). The use of Fürstner's conditions (*33*) proved to be critical to deliver dienoate **18** in a synthetically useful yield. Direct reduction of the C16-C17 olefin of dienoate **18** turned out to be formidable because many of the conditions tried led to reduction from the convex face of the molecule. This problem was circumvented by first treating dienoate **18** with in situ generated Co_2B (*34*) to afford exclusively tetrasubstituted olefin **19** (no reduction of C16-C17 or butenolide moiety was observed). A myriad of bases were tried to isomerize this olefin into conjugation, only to produce the wrong stereochemistry of the newly generated chiral center at C17. Ultimately, we found that heating **19** in the presence of Barton's base (*35*) delivered enoate **20** with a predominantly correct disposition of the butenolide moiety (*dr* = 3:1). Lastly, unmasking of all the hydroxyl groups under acidic condition delivered synthetic ouabagenin (**1**).

Salient features of the current route include (i) the application of solid-state Norrish type II photochemistry in natural product synthesis; (ii) chemoselective, reagent-controlled cyclobutanol fragmentation using an inexpensive reagent, N-iodosuccinimide; (iii) implementation of an "on-water" epoxide fragmentation; (iv) a highly selective olefin isomerization promoted by fluorous media; (v) a highly diastereoselective Mukaiyama hydration to furnish the requisite cis C/D ring junction; (vi) a chemoselective dienoate reduction with Co_2B; and (vii) robustness and scalability of the route in an academic setting (20 steps from andrenosterone, 0.56% overall yield, 77% average yield per step). Scalable complex molecule synthesis (gram scale or above) not only demonstrates feasibility but also ensures the robustness of the route, delivers useful quantities to biological collaborators, and lowers the barrier for pharmaceutical development. Despite being a semisynthetic approach, the current route is amenable to scaffold diversification: Preliminary studies suggest that opposite stereochemistry of both the C3 and C11 centers is readily accessible in a controlled fashion; the isolated olefin on **15** affords a platform for versatile functionalizations, including the introduction of heteroatoms, such as fluorine, with radical-based methods (showcased in Fig. 4A) (*36*); last, the late-stage Stille coupling represents yet another potential point of diversification by way of attachment of different heterocyclic domains at C17.

The synthesis of the highly oxidized natural product ouabagenin represents a proof of concept for the development of a retrosynthetic strategy centered solely on the synergistic union of redox and stereochemical relays. As illustrated in Fig. 4B, previous approaches to the semisynthesis of cardenolides (*5*, *6*, *37*) and related steroids (batrachatoxin) used indirect means to install crucial oxidized functionality at C19 and C14. In all three cases, this resulted in lengthy routes, compromising both the brevity and scalability of the syntheses. In contrast, by using a transform-based approach to "look ahead" (*38*), the C11 and C17 ketones were viewed as "redox donors" for the requisite oxidations at C19 and C14, respectively. This logic enabled a dramatic increase of complexity to be imparted on a minimally oxidized, readily available steroid. In a similar vein to synthesis designs predicated on minimizing protecting group chemistry (*39*) or maximizing aspects of synthesis economy (*40*), the primary purpose of this work was to generate opportunities to innovate. Although the ouabagenin case study reported here is only a single example, we anticipate that syntheses that incorporate such a strategic interplay will result in more efficient routes to terpenes.

References and Notes

1. R. Tschesche, *Proc. R. Soc. Lond. B Biol. Sci.* **180**, 187 (1972).
2. G. Rousseau, B. Breit, *Angew. Chem. Int. Ed.* **50**, 2450 (2011).
3. J. R. Hanson, *Nat. Prod. Rep.* **22**, 104 (2005).
4. Y. Ishihara, P. S. Baran, *Synlett* **12**, 1733 (2010).
5. K. Wiesner, T. Y. R. Tsai, *Pure Appl. Chem.* **58**, 799 (1986).
6. R. Imhof, M. E. Gössinger, W. Graf, H. Berner, L. Berner-Fenz, H. Wehrli, *Helv. Chim. Acta* **55**, 1151 (1972).
7. E. J. Corey, W. R. Hertler, *J. Am. Chem. Soc.* **81**, 5209 (1959).
8. K. C. Fortner, D. Kato, Y. Tanaka, M. D. Shair, *J. Am. Chem. Soc.* **132**, 275 (2010) and references cited therein.
9. J. Shi *et al.*, *J. Am. Chem. Soc.* **133**, 8014 (2011).
10. C. K. Jana *et al.*, *Angew. Chem. Int. Ed.* **50**, 8407 (2011).
11. A. Szent-Gyorgyi, *Chemical Physiology of Contraction in Body and Heart Muscle*, (Academic Press, New York, 1953), pp. 86–91.
12. A. Kawamura *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **96**, 6654 (1999).
13. D. D. Schocken, M. I. Arrieta, P. E. Leaverton, E. A. Ross, *J. Am. Coll. Cardiol.* **20**, 301 (1992).
14. Y. Kamano *et al.*, *Bioorg. Med. Chem.* **6**, 1103 (1998).
15. P. W. Erhardt, *J. Med. Chem.* **30**, 231 (1987).
16. H. Zhang, M. S. Reddy, S. Phoenix, P. Deslongchamps, *Angew. Chem. Int. Ed.* **47**, 1272 (2008).
17. B. Heasley, *Chem. Eur. J.* **18**, 3092 (2012).
18. H. Wehrli, M. S. Heller, K. Schaffner, O. Jäger, *Helv. Chim. Acta* **44**, 2162 (1961).
19. B. Vijayarahavan, S. M. S. Chauhan, *Tetrahedron Lett.* **31**, 6223 (1990).
20. D. Ng, Z. Yang, M. A. Garcia-Garibay, *Org. Lett.* **6**, 645 (2004).
21. N. G. Anderson, *Org. Process Res. Dev.* **16**, 852 (2012).
22. K. Wietzerbin, J. Bernadou, B. Meunier, *Eur. J. Inorg. Chem.* **2000**, 1391 (2000).
23. J. Barluenga, F. González-Bobes, M. C. Murguía, S. R. Ananthoju, J. M. González, *Chem. Eur. J.* **10**, 4206 (2004).
24. C. E. McDonald, H. Holcomb, T. Leathers, F. Ampadu-Nyarko, J. Frommer Jr., *Tetrahedron Lett.* **31**, 6283 (1990).
25. S. Hrycko, P. Morand, F. L. Lee, E. J. Gabe, *J. Org. Chem.* **53**, 1515 (1988).
26. R. C. Larock, *Comprehensive Organic Transformations* (Wiley, New York, 1989), pp. 505–508.
27. S. Narayan *et al.*, *Angew. Chem. Int. Ed.* **44**, 3275 (2005).
28. U. Egner *et al.*, *Tetrahedron* **55**, 11267 (1999).
29. C. Samojłowicz, M. Bieniek, A. Zarecki, R. Kadyrov, K. Grela, *Chem. Commun.* **2008**, 6282 (2008).
30. S. Isayama, T. Mukaiyama, *Chem. Lett.* **18**, 1071 (1989).
31. D. H. R. Barton, R. E. O'Brien, S. Sternhell, *J. Chem. Soc.* **1962**, 470 (1962).
32. G. J. Hollingworth, G. Perkins, J. Sweeney, *J. Chem. Soc. Perkins Trans.* **1996**, 1913 (1996).
33. A. Fürstner *et al.*, *Chem. Commun.* **2008**, 2873 (2008).
34. S.-K. Chung, *J. Org. Chem.* **44**, 1014 (1979).
35. D. H. R. Barton, J. D. Elliott, S. D. Géro, *J. Chem. Soc., Perkin Trans. 1* **1982**, 2085 (1982).
36. T. J. Barker, D. L. Boger, *J. Am. Chem. Soc.* **134**, 13588 (2012).
37. E. Yoshii, T. Oribe, K. Tumura, T. Koizumi, *J. Org. Chem.* **43**, 3946 (1978).
38. E. J. Corey, X.-M. Cheng, *The Logic of Chemical Synthesis* (Wiley, New York, 1989), p. 17.
39. P. S. Baran, T. J. Maimone, J. M. Richter, *Nature* **446**, 404 (2007).
40. T. Newhouse, P. S. Baran, R. W. Hoffmann, *Chem. Soc. Rev.* **38**, 3010 (2009).
41. H. Yeom, S. G. Sligar, H. Li, T. L. Poulos, A. J. Fulco, *Biochemistry* **34**, 14733 (1995).

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Supplementary Materials

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Materials and Methods
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