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Scalable C–H Oxidation with Copper: Synthesis of Polyoxypregnanes

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Supporting Information

ABSTRACT: Steroids bearing C12 oxidations are widespread in nature, yet only one preparative chemical method addresses this challenge in a low-yielding and not fully understood fashion: Schönecker's Cu-mediated oxidation. This work shines new light onto this powerful C–H oxidation method through mechanistic investigation, optimization, and wider application. Culminating in a scalable, rapid, high-yielding, and operationally simple protocol, this procedure is applied to the first synthesis of several parent polyoxypregnane natural products, representing a gateway to over 100 family members.

Given the sheer number of FDA-approved medicines and natural products containing their molecular skeleton, steroids are perhaps the most privileged complex structure in drug discovery.[1] A key differentiating feature among steroids is the myriad of different oxidation patterns expressed in their backbone. This "oxidation barcode" serves to modulate both their physical and biological properties.[2] As part of a continuing collaboration with LEO Pharma[3] to use two-phase terpene synthesis to solve complex chemical problems of medicinal relevance, natural products belonging to the utendin family (**1**–**3**, Figure 1A) were targeted.[4] Featured in a large number of polyoxypregnanes from *Asclepiadaceae* plants (>100 isolated), a clear opportunity for innovation resides in their unusual oxidation pattern, particularly at C12.[5] The C12 oxidation, found in numerous natural steroids of both terrestrial and marine origin, is a classic bottleneck for synthesis with a singular preparative chemical solution.[6g] The venerable Schönecker oxidation is still employed despite difficult experimental setup, poor yields, and long reaction times.[6] Here, a renovation of this C–H oxidation protocol and a reinvestigation of its scope and mechanism are applied to the first synthesis of several members of the utendin steroid family.

For strategic reasons discussed below, a steroidal Δ^6-*i*-diene (**4**, Figure 1B) was targeted as a surrogate for the homoallylic alcohol found in utendin-based systems. Since poor yields were obtained under Schönecker's original conditions, a conceptually new method for oxidizing the C12 position was initially sought. Thus, extensive efforts took place across various mechanistically distinct methods ranging from radical to transition-metal-mediated C–H activation.

Close proximity of the requisite C20 oxidation and its 1,5-relationship to the C12-β-C–H bond inspired all of the approaches. Given the success of a Norrish reaction in the context of a redox-relay approach to steroid oxidation, the C20 ketone was evaluated under a variety of photochemical conditions.[3b,c] Unfortunately, despite screening numerous

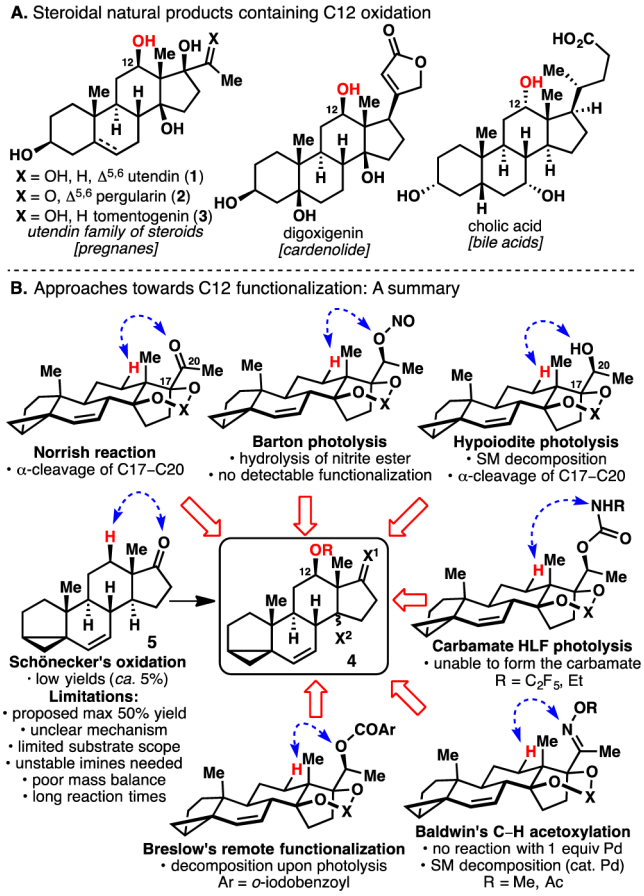

Figure 1. (A) Steroidal natural products containing oxidation at C12. (B) Attempted strategies toward directed C12 functionalization using reported chemistries.

solvents and photosensitizers, only undesired photocleavage products resulting from scission of the C17–C20 bond were obtained. Next, Barton's classic photolysis was evaluated in a variety of different solvents, but only the hydrolyzed nitrite ester was detected.[7] Similarly, other methods to generate the O-radical (hypoiodite photolysis, $Pb(OAc)_4/I_2$, AgOI) only resulted in decomposition or α-cleavage of the C17–C20 bond.[8] Attempts to generate a tethered radical were thwarted by the low reactivity of the C20 hydroxyl group, as we were unable to prepare the required carbamate for a Hofmann–Löffler–Freytag-type reaction (HLF).[9] Baldwin's Pd-mediated oxime-directed acetoxylation gave no reaction under both stoichiometric and catalytic

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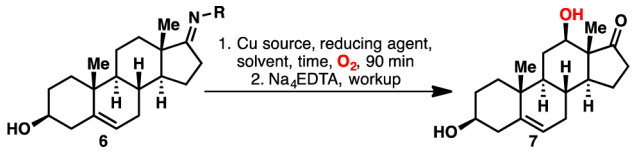
conditions.[10] Finally, extensive decomposition of the substrate was observed using Breslow's remote functionalization protocol.[11]

With this string of setbacks, our attention returned to Schönecker's oxidation protocol. Initially developed in 2003,[6a] this promising Cu-mediated C−H oxidation has been featured in a couple of stunning steroid syntheses, namely Shair's synthesis of cephalostatin[6d] and Giannis' synthesis of cyclopamine.[6e] Testament to its powerful ability to access the elusive C12 oxidation, it has been rapidly adopted in spite of its numerous shortcomings: long reaction times, poor mass recovery, limited substrate scope, a proposed 50% yield maximum detailed through studies by Schönecker,[6b,c] and a lack of detailed mechanistic understanding. *It is therefore somewhat puzzling that no attention has been paid to understanding and improving this incredibly useful and potentially practical Cu-based C−H oxidation system.*[12]

In the absence of a clear mechanistic picture, optimization efforts centered around modifications that would achieve conversion above the proposed maximum 50% threshold using dehydro-*epi*-androsterone (DHEA) as a model substrate (Table 1).[6b,c] Under Schönecker's original conditions (entries 1−2), low

Table 1. Reaction Development and Optimization[a]



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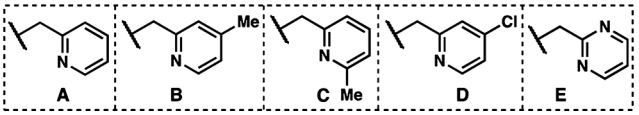
Entry	Cu source	Reductant	Solvent (conc.)	T/time (°C/h)	R	Yield (rsm)
1[b]	$Cu(MeCN)_4PF_6$	none	acetone	23/ 24	A	20% (36%)[d]
2[b]	$Cu(OTf)_2$	benzoin, Et_3N	acetone	23/ 24	A	35% (22%)[d]
3	$Cu(MeCN)_4PF_6$	none	acetone (0.02 M)	50/ 1.5	A	45% (35%)[c]
4	$Cu(MeCN)_4PF_6$	benzoin, Et_3N	acetone (0.02 M)	50/ 1.5	A	21% (42%)[c]
5	$Cu(MeCN)_4PF_6$	$FeBr_2$	acetone (0.02 M)	50/ 1.5	A	54% (26%)[c]
6	$Cu(MeCN)_4PF_6$	Zn powder	acetone (0.02 M)	50/ 1.5	A	58% (5%)[c]
7	$Cu(MeCN)_4PF_6$	Et_3SiH	acetone (0.02 M)	50/ 1.5	A	29% (37%)[c]
8	$Cu(MeCN)_4PF_6$	Na ascorbate	acetone (0.02 M)	50/ 1.5	A	67% (17%)[d]
9	$Cu(MeCN)_4PF_6$	Na ascorbate	acetone (0.15 M)	50/ 1.5	A	75%[c]
10	$Cu(MeCN)_4PF_6$	Na ascorbate	acetone:MeOH[e]	50/ 1.5	A	66%[d]
11	**$Cu(OTf)_2$**	**Na ascorbate**	**acetone:MeOH[e]**	**50/ 1.5**	**B**	**68% (5%)[d]**
12	**$Cu(MeCN)_4PF_6$**	**Na ascorbate**	**acetone:MeOH[e]**	**50/ 1.5**	**B**	**90% (5%)[d]**
13	$Cu(MeCN)_4PF_6$	none	acetone (0.02 M)	50/ 1.5	C	trace[c]
14	$Cu(MeCN)_4PF_6$	none	acetone (0.02 M)	50/ 1.5	D	trace[c]
15	$Cu(MeCN)_4PF_6$	none	acetone (0.02 M)	50/ 1.5	E	trace[c]



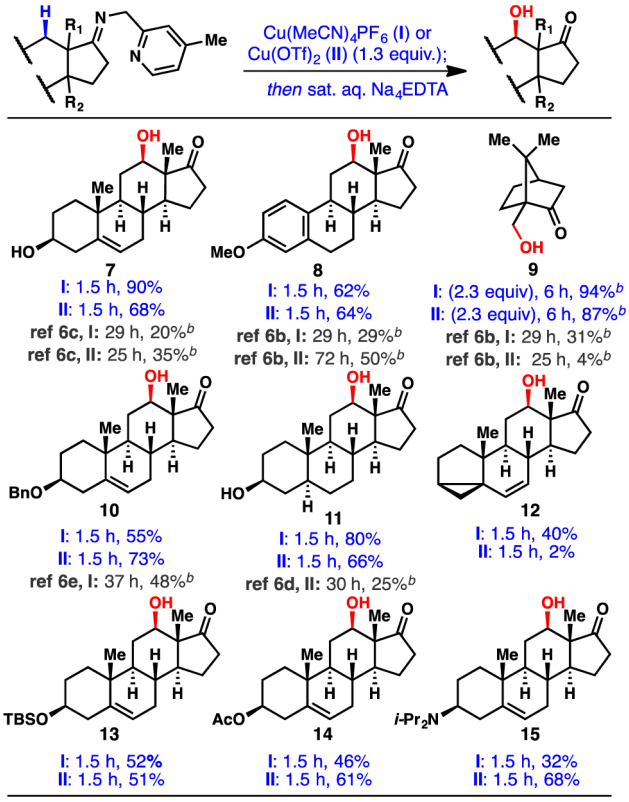
[a]**6** (0.5 mmol), Cu source (1.3 equiv), reductant (2.0 equiv), under O_2 for 1.5 h. [b]Reaction run for 24 h. [c]NMR yields using CH_2Br_2 as internal standard. [d]Isolated yields. [e]0.15 M.

conversion of **6** to **7** was accompanied by poor mass recovery (ca. 55−60%). Despite much effort, the structure of the remaining material was not identifiable; however, by simply heating the same reaction to 50 °C (entry 3), the overall mass recovery could be improved to ca. 80% (7 + DHEA) in only 1.5 h.

It was next reasoned that an effective reducing agent might achieve recycling of the postulated Cu(II) end species in this oxidative reaction. Cu(I) was used for this screen for operational simplicity. Numerous reducing agents were evaluated (entries 4−8), and it was rapidly apparent that this variable was key to improving the reaction. Indeed, the use of either $FeBr_2$ or Zn furnished a >50% yield of **7**, a milestone in that it surpassed the proposed 50% "limit". Sodium ascorbate, a reducing agent routinely employed in the CuAAC reaction developed by Sharpless et al., emerged as the best candidate (entries 8−12) with both Cu(I) and Cu(II)-based systems.[13] Furthermore, the addition of MeOH provided improved conversions (entry 10). An array of different imines was prepared (**A**−**E**) with imine **B** emerging as the best. Taken together, these improvements enabled a near quantitative yield of **7** in only 90 min. Notably the revised procedure is truly "dump-and-stir", circumventing the laborious premixing, incubation, and complex workup required previously.

To date, only four types of ketone-derived substrates have been enlisted in Schönecker's C−H oxidation. The optimized procedure derived herein proved superior across all of these substrates in both isolated yields and reaction time (Table 2).

Table 2. Scope of Directed Hydroxylation[a]



[a]Conditions: Cu (1.3 equiv), sodium ascorbate (2.0 equiv), acetone/methanol (1:1, c = 0.15 M), 50 °C, O_2. [b]Imine **A** was used.

The conditions are compatible with silyl ethers (**13**), esters (**14**), and tertiary amines (**15**). Returning to the original objective of this work, implementation of the new oxidation conditions with Cu(I) enabled C12 oxidation of the highly functionalized steroidal Δ^6-*i*-diene (**12**), a critical starting material for the synthesis of utendin (*vide infra*).

A series of NMR studies was conducted to gain mechanistic insight into the reaction (Figure 2). Initial studies with substoichiometric amounts of $Cu(OTf)_2$ (0.5 equiv) and sodium ascorbate (1.5 equiv) led to no observable C12 oxidation over 60 min suggesting that the previously proposed $[Cu_2O_2]$−substrate dimer complex is unlikely to be responsible for the reactivity seen in this system.[6b,c] Oxidation was only detected (~12% at 120 min) after further $Cu(OTf)_2$ (0.25 equiv) was titrated into the

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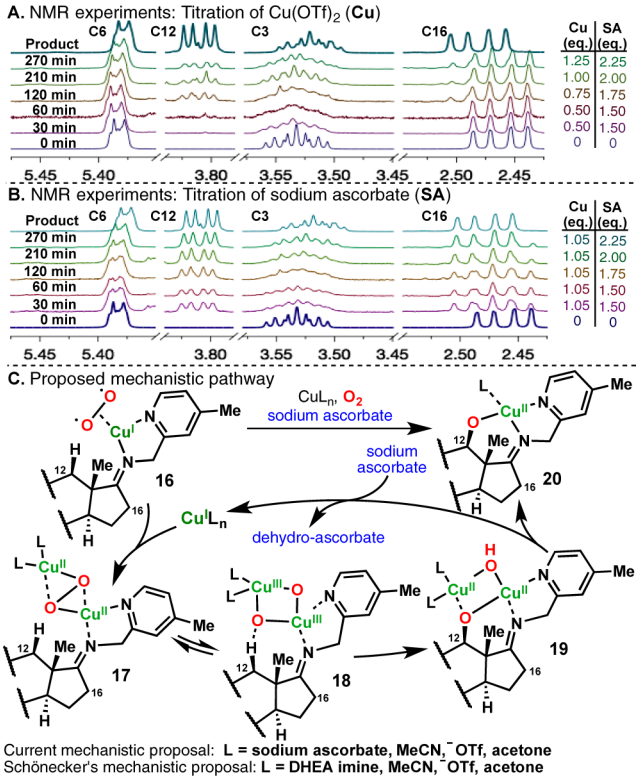


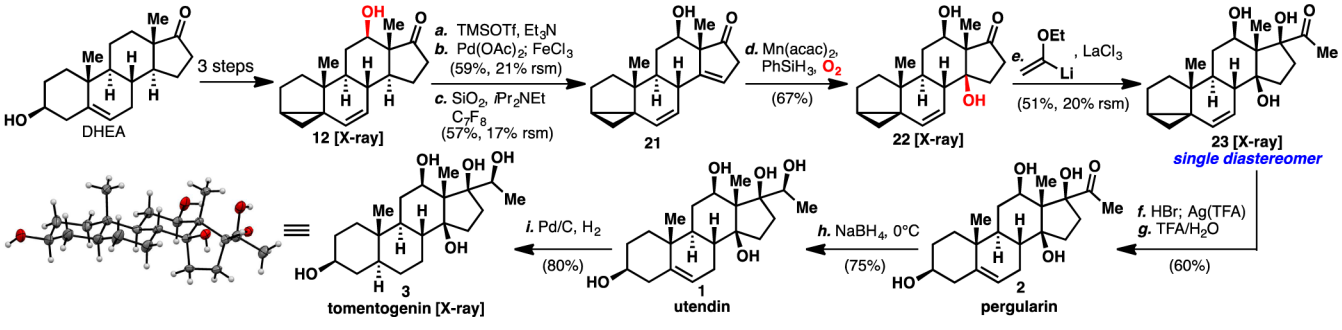
Figure 2. NMR studies of (A) Cu titration and (B) sodium ascorbate titration. (C) Revised mechanistic proposal.

reaction. Additional $Cu(OTf)_2$ (0.5 equiv) and sodium ascorbate (1.0 equiv) added over 2.5 h led to a minor increase in conversion. In stark contrast, titration of sodium ascorbate into a solution of substrate and a slight excess of $Cu(OTf)_2$ (1.05 equiv) gave 50% conversion to product in only 30 min. Additional sodium ascorbate (0.75 equiv) over 3.5 h allowed for near complete conversion.

A new mechanistic picture that is consistent with the observed data is shown in Figure 2C. Following initial Cu binding to give **16**, additional uncoordinated Cu(I) and O_2 could complex to form the imine complex **17**, a $[Cu_2O_2]$ species.[6c,14] The active Cu-species is likely the bis(μ-oxo)dicopper(III) complex **18**,[14] but it could also be a mixed bis(μ-oxo)Cu(II)/Cu(III) complex.[15] Oxidation of the proximal C−H bond then presumably occurs through an oxygen-rebound mechanism.[6c,16] The resulting Cu(II) that is not directly ligated to the substrate in the $[Cu_2O_2]$ complex **19** is then reduced by ascorbate to Cu(I) and released, allowing for further substrate engagement.[17] Besides acting as a reductant, ascorbate could also participate as a weak ligand to copper.[18] The remaining Cu(II)/pregnane tridentate complex **20** is presumably stable and inert to further oxidations. Despite repeated attempts by Schönecker and us, we were not successful in obtaining X-ray quality crystals of any of the proposed intermediates.

Armed with a scalable and robust C12 oxidation, the first synthesis of complex polyoxypregnanes was accomplished (Scheme 1). The use of a Δ^6-*i*-diene to mask the A-ring functionality of a steroid as part of a synthesis is a strategic decision without precedent. Such a construct was chosen to minimize protecting group fluctuations and chemoselectivity concerns during the ensuing redox-relay. The synthesis commenced with inexpensive DHEA (ca. $3/gram), which is transformed to Δ^6-*i*-diene via triflation and elimination (35%).[19] The remaining mass balance was accounted for by an ammonium adduct by the attack of triethylamine into the allylic triflate (see SI for structure). Next, the Cu-mediated C−H oxidation was employed on gram-scale as discussed above to deliver **12** in 40% yield. Saegusa oxidation (59%) followed by a recently developed olefin isomerization protocol[3a] (57%) delivered the diene **21**. Stereo- and chemoselective Mukaiyama hydration took place smoothly to furnish diol **22** in 67% yield as verified by X-ray crystallography.[3a] The D-ring methyl ketone subunit was then installed using an organolanthanum reagent derived from lithiated ethyl vinyl ether in 51% yield (along with 20% recovered **22**).[20] At this juncture, the allylic cyclopropane, which remained chemically silent until this point, was cleanly dismantled using HBr to afford the homoallylic bromide.[21] Silver-assisted solvolysis followed by acid treatment produced the natural product pergularin **2** (60% over 3 operations). From this point, two additional natural polyoxypregnanes were accessed by sequential stereoselective reductions. $NaBH_4$ treatment of **2** delivered utendin, **1** (75%), which could then be hydrogenated over Pd/C to tomentogenin, **3** (80%). The structure of tomentogenin was unambiguously confirmed by X-ray crystallography. Over 100 natural products with promising bioactivity can, in principle, be accessed from these three parent natural products, differing only in the location and identity of various

Scheme 1. Synthesis of utendin (1), pergularin (2), and tomentogenin (3)[a,b]



[a]Reagents and conditions: (a) TMSOTf, Et_3N, CH_2Cl_2, 0 °C; (b) $Pd(OAc)_2$, MeCN, 23 °C, 24 h; $FeCl_3$; K_2CO_3 (59%, rsm 21%); (c) SiO_2, iPr_2NEt, C_7F_8, 24 h, (57%, rsm 17%); (d) $Mn(acac)_2$, $PhSiH_3$, PPh_3, O_2, EtOH, 3 h, (67%); (e) (1-ethoxylvinyl)lithium, $LaCl_3$·2 LiCl, THF, −78 °C, 5 h (51%, 20% rsm); (f) HBr, AcOH, EtOAc, 15 min; AgTFA, H_2O; (g) TFA, THF/H_2O, 24 h (60% over 3 steps); (h) $NaBH_4$, MeOH, 0 °C (75%, 5:1 dr); (i) Pd/C, H_2, MeOH, 23 °C, 24 h, (80%, 5:1 dr). [b]See SI for X-ray structures.

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ester and sugar side chains. Such studies are ongoing and now enabling biological inquiries at LEO Pharma.

The fascinating Cu-mediated Schönecker oxidation, the only practical solution to the challenge of site-specific steroidal C12 functionalization, has been reinvestigated and dramatically improved. The new imine directing group and alternative reducing agent render this an operationally simple reaction that is no longer limited to a 50% maximum yield with long reaction times. The newly developed C−H oxidation protocol was studied mechanistically and applied to a range of additional substrates, including a key intermediate for the first synthesis of polyhydroxylated pregnanes belonging to the utendin class (**1**−**3**). Salient features of this synthesis involve the inaugural use of a Δ^6-*i*-diene in complex steroid synthesis and stereoselective redox-relay events.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b09463.

Experimental procedures and X-ray crystallographic data (PDF)
Compound spectra (PDF)
Crystallographic data (CIF)
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Notes

The authors declare no competing financial interest.

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