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Stereoselective semisynthesis of uzarigenin and *allo*-uzarigenin†

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Herein, we report the concise semisynthesis of the natural cardenolide uzarigenin and its diastereoisomer *allo*-uzarigenin in nine and seven steps, respectively, starting from the broadly available *epi*-androsterone. For this purpose, the synthetic strategy for the stereoselective introduction of the β-hydroxy group at C-14 *via* Mukaiyama oxidation is discussed. Additionally, the installation of the butenolide ring at C-17 is performed using a Stille-cross-coupling reaction with subsequent stereoselective hydrogenation of the C-16/C-17 double bond to exclusively give *allo*-uzarigenin. By directing the hydrogenation *via* a protecting group strategy, the C-17β isomer can also be obtained stereoselectively.

Introduction

Uzarin (**1**) and its aglycone uzarigenin (**2**) belong to the natural product class of cardiac glycosides, and have been known for their medicinal use since centuries (Fig. 1).[1] They can be obtained from the Uzara plant (*Xysmalobium undulatum*), which belongs to the milkweed family (*Asclepiadoideae*). In African folk medicine, the extracts isolated from the Uzara root were used for a long time to treat wounds, diarrhea, spasms, menstrual cramps, and headaches. Unlike other cardiac glycosides such as digitoxin (**3**), Uzara glycosides have a low cardiotonic effect, making intoxication less likely to occur.[2–4] Uzarin (**1**) and its aglycone uzarigenin (**2**) exhibit several structural characteristics of the steroid class of cardiac glycosides, such as the β-orientated unsaturated lactone ring at C-17 and the β-hydroxy group at C-14, resulting in a *cis*-fusion of the C/D rings. Like many other cardiac glycosides derived from the plant family of *Asclepiadoideae*, they feature a typical *trans* A/B ring junction, whereas most other cardiac glycosides, such as the well-investigated digitoxin (**3**), have *cis*-fused A/B rings.[5] Uzarigenin (**2**), therefore, can be assigned to the 5α-configured family of cardenolides, to which the better-known calotropin (**4**) also belongs.

The correspondence of concurrent reactions in the two configurationally and energetically different series (5α and 5β) is not self-evident. For example, a reaction sequence leading to digitoxigenin in the 5β-series is not generally transferable to the 5α-series.[6] Nevertheless, Kurt Radscheit and co-workers succeeded in converting 15α-hydroxy-cortexon into 3-oxo-5α-carda-14,20(22)-dienolide and claimed to have successfully synthesized uzarigenin (**2**) *via* two different synthetic routes. However, the stereochemistry at C-14 was not further discussed.[7] The same applies to Khristulas' uzarigenin (**2**) semisynthesis, which started from 3β-acetoxy-5α-pregn-16-en-20-one and did not provide any direct proof of the configuration of the synthesized compounds.[8] Emil Angliker managed to

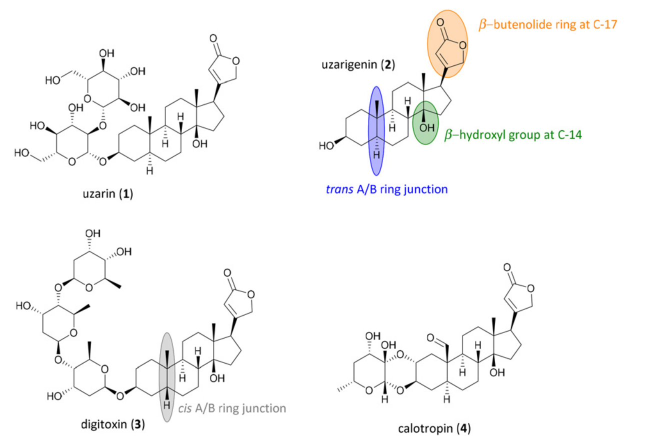

Fig. 1 Molecular structures of the cardiac glycosides uzarin (**1**), its aglycone uzarigenin (**2**), digitoxin (**3**) and calotropin (**4**).

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introduce a 14β-hydroxy group but struggled with the configuration at C-17 and, therefore, could only report the synthesis of *allo*-uzarigenin.[9] Wicha *et al.* investigated the D ring chemistry in more detail and achieved the stereoselective synthesis of 3-OMe uzarigenin; however, the introduction of the butenolide ring at C-17 in the β-position involved 13 steps and the ether moiety at C-3 was not removed at the end of the sequence.[10,11]

So far, uzarigenin (**2**) with unambiguously correct stereochemistry can only be obtained with the support of nature: for example, Bauer and Gonzalez were able to extract uzarigenin (**2**) from *Asclepias syriaca* L. or leaves of *Scrophulariaceae*.[12,13] Sauer *et al.* instead used *Strophanthus kombé*, a member of the *Apocynaceae* family, to convert 5α-pregnanolone into uzarigenin (**2**) *via* a foliar application method.[14,15] Okada and Anjyo successfully converted the more widely occurring digitoxigenin to uzarigenin (**2**) *via* epimerization at the C-5 position.[16]

Besides these nature-supported methods, none of the pioneering syntheses described earlier give access to the natural version of uzarigenin (**2**) and the syntheses suffer furthermore from quite lavish procedures and a lack of stereocontrol. Therefore, we aimed to develop a straight and high-yielding synthesis route, which puts emphasis on well-characterized compounds by using 2D NMR spectra and X-ray analysis for the efficient semisynthesis of uzarigenin (**2**) and its C-17 epimer *allo*-uzarigenin (**21**).

Results and discussion

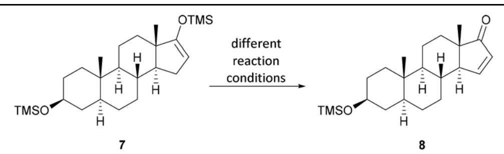
Inexpensive and readily available *epi*-androsterone (**5**) was chosen as the starting material for the semisynthesis of uzarigenin (**2**), requiring the introduction of the butenolide ring at C-17 and the inversion of the stereogenic center at C-14. To substitute the hydrogen atom attached in the α-position at C-14 with the aimed β-hydroxyl group, a three-step sequence was envisioned, with the first step comprising the synthesis of the Michael system **8**. As presented in Scheme 1, *epi*-androsterone (**5**) was lithiated at −78 °C and subsequently the TMS enol ether **7** was formed by adding trimethylsilyl chloride.

Without further purification, the enol ether **7** was subjected to the Saegusa–Ito oxidation, which is a well-known method for steroid compounds.[17–23] However, most of the procedures use stoichiometric amounts of palladium, although many reoxidants have been described in the literature, including copper(II) salts such as copper(II) acetate or copper(II) chloride, 1,4-benzoquinone, oxygen, and Oxone®.[24–28] With the aim of using palladium in catalytic amounts, different reaction conditions were screened, focusing on inexpensive oxygen and copper(II) acetate as reoxidants (see Table 1 and Table SI-1 in the ESI†).

Using catalytic amounts of palladium and oxygen or copper (II) acetate as the reoxidant, comparable yields to that obtained when using stoichiometric amounts of palladium could be obtained (entries 1–3). Varying the solvent apparently influenced the yield, with a mixture of CH_2Cl_2/DMSO achieving the highest yields (entries 5 and 6). A further decrease in the catalyst amount resulted in only a minor drop in yield (compare entries 5 and 8). Furthermore, no reaction took place without palladium(II) acetate (entry 7), proving the latter to be the active metal in the reaction. The use of copper(II) chloride, Oxone® or 1,4-benzoquinone as the reoxidant did not give any further improvement in yields (see ESI Table SI-1†).

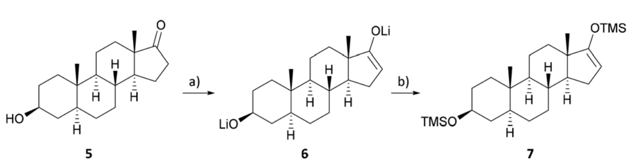
The rearrangement of the conjugated Δ^{15} to the isolated Δ^{14} double bond has already been effectively applied in many natural product syntheses[17–21,29] and should once more serve as a starting point for the introduction of the C-14 hydroxy group in this work. Analogously to Johns *et al.*,[17,30–32] isomerization was carried out with *p*-toluene sulfonic acid in refluxing toluene to give the desired product **9** in 61% yield after a reaction time of 15–20 minutes (Scheme 2).

Table 1 Investigation of the optimal reaction conditions for the synthesis of the Michael system **8** using palladium(II) acetate as a catalyst

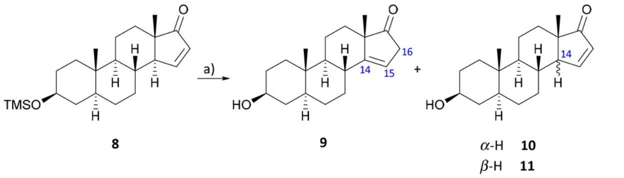


Entry	Reagents[a]	Reaction conditions	Isolated yield [%]
1	$Pd(OAc)_2$ [b]	CH_2Cl_2/MeCN (3 : 1), r.t., 16 h	48
2	$Pd(OAc)_2$, $Cu(OAc)_2$	CH_2Cl_2/MeCN (2 : 3), r.t., 24 h	43
3	$Pd(OAc)_2$, O_2	CH_2Cl_2/MeCN (2 : 3), r.t., 24 h	39
4	$Pd(OAc)_2$, $Cu(OAc)_2$	MeCN, 60 °C, 24 h	45
5	**$Pd(OAc)_2$, $Cu(OAc)_2$**	**CH_2Cl_2/DMSO (2 : 3), r.t., 24 h**	**66**
6	**$Pd(OAc)_2$, O_2**	**CH_2Cl_2/DMSO (2 : 3), r.t., 24 h**	**62**
7	$Cu(OAc)_2$, O_2	CH_2Cl_2/DMSO (2 : 3), r.t., 24 h	0
8	$Pd(OAc)_2$, $Cu(OAc)_2$ [c]	CH_2Cl_2/DMSO (2 : 3), r.t., 24 h	55

[a] 20 mol% $Pd(OAc)_2$ and 40 mol% $Cu(OAc)_2$ were used if not stated otherwise. [b] 1.00 equiv. of $Pd(OAc)_2$ were used. [c] 10 mol% $Pd(OAc)_2$ and 15 mol% $Cu(OAc)_2$ were used.



Scheme 1 Synthesis of the precursor for the Saegusa–Ito oxidation. (a) LDA, THF, −78 °C, 1 h; (b) TMSCl, NEt_3, −78 °C to r.t., 1.5 h.



Scheme 2 Rearrangement reaction at the steroidal D ring double bond. (a) *p*-TsOH, toluene, 130 °C, 15–20 min, 61% (**9**).

In the course of this, deprotected starting material **10** and its 14β-epimer **11** could also be isolated by column chromatography on silica gel and reused for the rearrangement reaction. The molecular structure of **11** could be determined by X-ray crystallographic analysis (see the ESI†).

Starting from the isolated Δ^{14} double bond, the following step aimed to diastereoselectively attach the hydroxy group at C-14 in the β-position. Epoxidation with subsequent ring opening indicated the formation of many different products, and thus the Mukaiyama oxidation should accomplish the installation of the tertiary hydroxy group.[33–36] To investigate whether diastereoselectivity can be observed for this reaction, a wide range of reaction conditions were tested by varying the catalyst, solvent, additives, reaction time and the addition rate and amount of the reductant (see Table 2 and Table SI-2 in the ESI†).

For the Mukaiyama oxidation of **9**, no product formation could be observed in non-anhydrous 1,4-dioxane, making the use of an absolute solvent crucial (entries 1 and 2). Increasing the amount of reductant and adding molecular sieves to the reaction mixture resulted in a slight improvement in the yield from 44% to 53% (entry 3). To prevent the oxidation of the secondary hydroxyl group at C-3 as a possible side reaction, a TBDMS protecting group was introduced at C-3 prior to the oxidation, which led to a significant increase in the yield from 53% to 64% (entry 4). Unfortunately, an inseparable mixture of both hydroxy epimers was obtained in all experiments described above. The ratio of epimer A to epimer B was determined to be 2 : 1 by integration of the resonances of the angular methyl protons in the ^{1}H NMR spectra. Considering the improved yield, a benzyl-protecting group was introduced at C-3, which enabled the separation of the two epimers (entry 5), whose absolute configuration was determined by X-ray crystallographic analysis (see Fig. 2), and the desired 14β-epimer **16** was identified as the main product. Having the two epimers separated and assigned, the reaction was further optimized in terms of yield and particularly the diastereomeric ratio. Varying the catalyst or adding PPh_3[37] as an additive did neither improve the yield nor the diastereomeric ratio significantly (entries 6–8). Moreover, contrary to the literature,[38] no reaction took place at all with Co(III) or Mn(III) species (Table SI-2 in the ESI†). Ultimately, varying the solvent not only improved the yield (entries 9 and 12), but the use of a polar protic solvent also shifted the diastereomeric ratio sig-

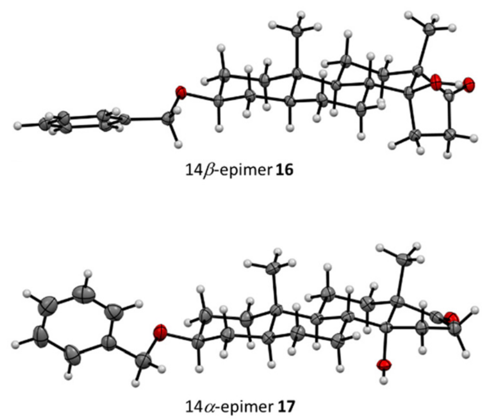
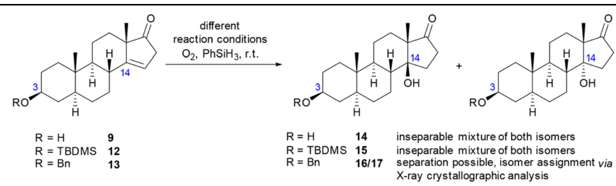


Fig. 2 Crystal structures of **16** and **17** (displacement parameters are drawn at the 50% probability level). The impact of the β-position of the C-14 substituent can be observed clearly: the 14α-epimer is mostly flat due to its all-*trans* ring linkages, while the 14β-epimer exhibits a more bowed shape due to the *cis*-linkage of the C-/D-rings.

Table 2 Optimization of the reaction conditions for the Mukaiyama oxidation of 9, 12 and 13



Entry	R	$PhSiH_3$ (equiv., a.r.)	Catalyst	Solvent	Additive	Reaction time	Yield [%], dr (β-OH : α-OH)
1	H	3.0, 1 h	$Co(acac)_2$	1,4-Dioxane[a]	—	3 h	0
2	H	3.0, 1 h	$Co(acac)_2$	1,4-Dioxane[b]	—	3 h	44
3	H	4.5, 2 h	$Co(acac)_2$	1,4-Dioxane[b]	4 Å MS	20 h	53
4	TBDMS	4.5, 2 h	$Co(acac)_2$	1,4-Dioxane[b]	4 Å MS	20 h	64
5	Bn	4.5, 2 h	$Co(acac)_2$	1,4-Dioxane[b]	4 Å MS	20 h	62 (2.0 : 1)
6	Bn	4.5, 2 h	$Co(dpm)_2$	1,4-Dioxane[b]	4 Å MS	20 h	49 (2.0 : 1)
7	Bn	4.5, 2 h	$Mn(acac)_2$	1,4-Dioxane[b]	4 Å MS, PPh_3[c]	20 h	33 (2.3 : 1)
8	Bn	4.5, 2 h	$Co(acac)_2$	1,4-Dioxane[b]	4 Å MS, PPh_3[c]	20 h	60 (2.1 : 1)
9	Bn	4.5, 2 h	$Co(acac)_2$	MeCN[b]	4 Å MS	20 h	71 (2.4 : 1)
10	Bn	4.5, 2 h	$Co(acac)_2$[d]	MeCN[b]	4 Å MS	20 h	59 (2.5 : 1)
11	Bn	4.5, 2 h	$Co(acac)_2$	MeOH[b]	3 Å MS	20 h	45[e] (4.7 : 1)
12	**Bn**	**4.5, 2 h**	**$Co(acac)_2$**	**EtOH**[b]	**4 Å MS**	**20 h**	**73 (9.4 : 1)**

Reaction conditions: catalyst (30 mol%); yields refer to the isolated mixture; the diastereomeric ratio was determined by integration of the resonance of the angular methyl group C-18 in the ^{13}C NMR spectra of the isomer mixture after prolonged relaxation delay ($d1$ = 10 s). [a] HPLC quality. [b] Absolute solvent. [c] 2.00 equiv. of PPh_3 were used. [d] 10 mol% $Co(acac)_2$ was used. [e] No full conversion. a.r. rate of addition.

nificantly from 2.0 : 1 to 4.7 : 1 for MeOH (entry 11) and eventually gave a dr of 9.4 : 1 in favour of the desired epimer **16** when ethanol was used as the solvent (entry 12).

After the successful diastereoselective introduction of the hydroxy group at C-14, the lactone ring has to be diastereoselectively attached to C-17. Thus ketone **16** was converted to the respective vinyl iodide **18** by following Barton's procedure.[39] For this purpose, the carbonyl functionality was treated successively with hydrazine and iodine to yield vinyl iodide **18** in 51% yield (Scheme 3). The sp^2-hybridized C-17 could now undergo a cross-coupling reaction following the procedure developed by Stille *et al.*,[40] which has also been successfully applied by us previously,[41] yielding cardadienolide **20** in 67% yield.

Cardadienolide **20** should then undergo a chemo- and diastereoselective reduction of the Δ^{16} double bond with simultaneous removal of the benzyl protecting group at C-3 using palladium on carbon as a catalyst. The reaction indeed proceeded diastereoselectively, as the formation of only one isomer was observed. Unfortunately, the reduction yielded the undesired isomer (*allo*-uzarigenin (**21**)) in 76% yield, which is consistent with the literature.[42,43] In comparison, the exclusive formation of the desired C-17β isomer was observed upon hydrogenation of 3β-hydroxy-5α,14α-carda-(16,20)-dienolide (**SI-06**, see the ESI†), suggesting a directing effect of the hydroxy group in the present substrate **20**. The stereochemistry at C-17 of **21** was determined by NOE correlation between the angular 18-CH_3 and 17-CH as shown in Fig. 3. Precise tuning

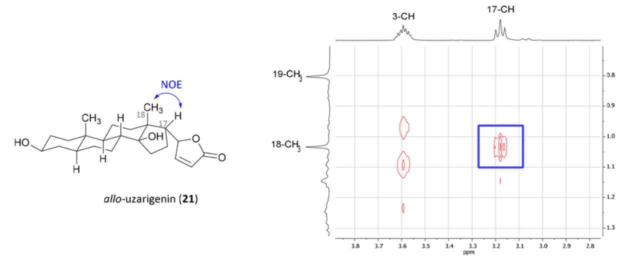
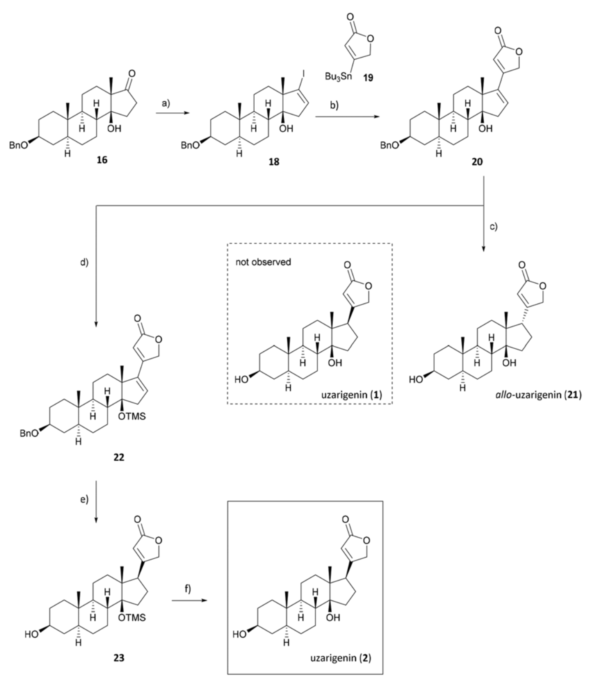


Fig. 3 Excerpt from the NOESY spectrum of *allo*-uzarigenin (**21**). A strong NOE correlation between 18-CH_3 and 17-CH indicates spatial proximity and thus hydrogenation from the β-face.

of the reaction time is mandatory for a chemoselective reaction since longer reaction times also result in a reduction of the double bond within the lactone ring, evident from the loss of the olefinic proton at δ = 5.77–5.83 ppm as shown for the C-14α-H system **SI-07** in the ESI.†

Since the hydrogenation of Δ^{16}-olefin **20** occurred from the convex β-face, affording exclusively the C-17α product (*allo*-uzarigenin (**21**)), TMS protection of the C-14 hydroxy group was conducted to circumvent a possible directing effect of the hydroxy group while introducing an even greater steric hindrance to the β-face at the same time (Scheme 3).[42,44,45] A subsequent reduction of **22** gave exclusively the desired C-17β product, which yielded the natural product uzarigenin (**2**) after acidic deprotection with 3 M HCl. The stereochemistry at C-17 was determined by 2D NOESY spectroscopy as shown in Fig. 4. NOE correlation between 22-CH and 18-CH_3 indicates spatial



Scheme 3 Synthesis of uzarigenin (**1**) and *allo*-uzarigenin (**21**). (a) N_2H_4, NEt_3, EtOH, 50 °C, 16 h; I_2, NEt_3, THF, 0 °C to r.t., 3 d, 51%; (b) $Pd(PPh_3)_4$, LiCl, CuCl, DMF, 60 °C, 24 h, 67%; (c) H_2, Pd/C (10 wt%), EtOAc, r.t., 30 min, 76%; (d) TMSCl, imidazole, DMF, r.t., 16 h, 94%; (e) H_2, Pd/C (10 wt%), EtOAc, r.t., 30 min, 62%; (f) 3 M HCl, MeOH, r.t., 4 h, 79%.

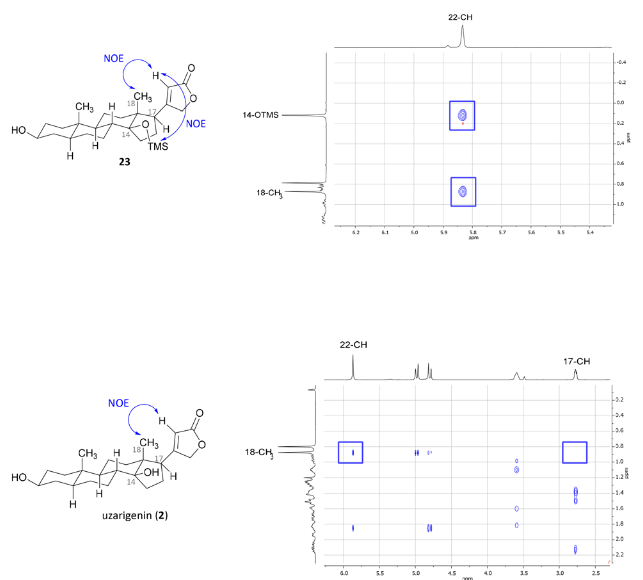


Fig. 4 Excerpt of the NOESY spectra of TMS protected uzarigenin **23** (top) and uzarigenin (**2**) (bottom). In both cases, a clear NOE correlation between 22-CH and 18-CH_3 indicates spatial proximity of the lactone ring and the 18-methyl group. Furthermore, a NOE cross peak between 22-CH and 14-OTMS can be seen, which further supports the successful hydrogenation from the α-face.

proximity of the lactone ring and the 18-methyl group and thus the successful hydrogenation from the α-face. Furthermore, no NOE correlation between 17-CH und 18-CH_3 can be seen, as exemplarily shown for the NOESY spectrum of uzarigenin (**2**). Moreover, the analytical data of *allo*-uzarigenin (**21**) and uzarigenin (**2**) synthesized in this work were compared with those from the literature and are in agreement (Tables SI-3–SI-5 in the ESI†).

Experimental section

The synthetic procedures for all synthesized compounds are available in the ESI.†

Conclusions

In summary, we have reported the first stereoselective semisynthesis of uzarigenin (**2**) and *allo*-uzarigenin (**21**) starting from the widely available *epi*-androsterone (**5**) in nine and seven steps, respectively. This synthesis route offers efficient access to uzarigenin (**2**) by using moderate to high-yielding stereoselective reactions. Correct stereochemistry was confirmed by 2D NMR experiments and X-ray analysis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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