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Enantioselective Total Synthesis of Cannogenol-3-*O*-α-L-rhamnoside via Sequential Cu(II)-Catalyzed Michael Addition/Intramolecular Aldol Cyclization Reactions

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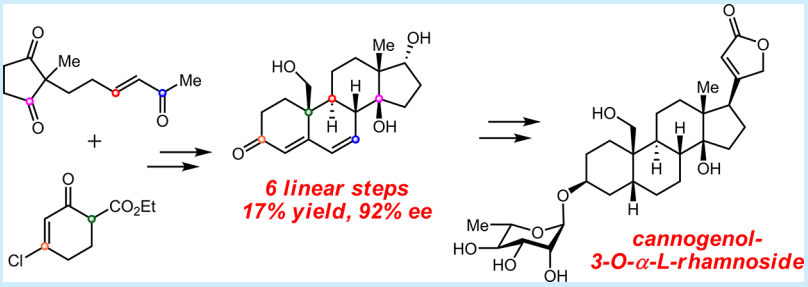
Supporting Information



ABSTRACT: A concise and scalable enantioselective total synthesis of the natural cardenolides cannogenol and cannogenol-3-*O*-α-L-rhamnoside has been achieved in 18 linear steps. The synthesis features a Cu(II)-catalyzed enantioselective and diastereoselective Michael reaction/tandem aldol cyclization and a one-pot reduction/transposition, which resulted in a rapid (6 linear steps) assembly of a functionalized intermediate containing C19 oxygenation that could be elaborated to cardenolide cannogenol. In addition, a strategy for achieving regio- and stereoselective glycosylation at the C3 position of synthetic cannogenol was developed and applied to the preparation of cannogenol-3-*O*-α-L-rhamnoside.

Cardiotonic steroids represent a large and important family of natural steroids that exhibit a wide spectrum of biological activities. The majority of these compounds are potent Na^+/K^+ ATPase inhibitors, a feature that makes them of great value for the treatment of various heart-associated diseases.[1] Cardiotonic steroids are secreted endogenously and used for the regulation of essential life processes such as renal sodium pressure, sodium transport, arterial pressure, cell growth differentiation, apoptosis, fibrosis, immunity, carbohydrate metabolism, and various central nervous functions.[2] The unique biological properties often coupled with challenging structural features prompted numerous semisynthetic and synthetic efforts toward the preparation of various cardiotonic steroids and their analogs.[3] These studies have resulted in many creative solutions that have enabled medicinal chemistry studies on many natural cardiotonic steroids and their analogs. These advances, however, are difficult to translate into the synthesis of highly oxygenated cardiotonic steroids, in particular, those carrying O atoms at the C1, C11, C12, and C19 positions. Not surprisingly, many of these challenging targets have only been synthesized in the past decade.[4]

Our group has long-standing interests in developing concise synthetic approaches to cardiotonic steroids.[5] Recently, we described a concise approach to the cardenolide core that is based on sequential enantioselective Cu(II)-catalyzed Michael/intramolecular aldol cyclization reactions (Figure 1B).[5a] This strategy enabled rapid enantioselective formation of cardiotonic steroid skeleta (i.e., **6**) featuring the oxidized C14 and C19 positions, but lacking the required oxygenation at the C3 position. Based on these studies, a new approach that was based on diastereoselective Michael reaction/intramolecular aldol cyclization of the functionalized β-ketoester **7** and enone **8** was developed.[5c] The resultant annulated product could be rapidly advanced to the fully functionalized steroidal core **9**. This steroidal intermediate was subsequently elaborated to the natural cardenolides 19-hydroxysarmentogenin and the trewianin aglycone bearing oxygenation at the C3, C11, C14, and C19 positions. These results suggest that Cu(II)-catalyzed Michael addition/Aldol cascade represents a powerful and straightforward method for achieving fast and selective syntheses of cardiotonic steroids with various oxidation patterns. To further demonstrate the generality and utility of this approach, our group targeted steroids possessing the C19 hydroxylation, but lacking the C11 hydroxyl group. This oxidation pattern is commonly found in various cardenolides including cannogenol (**2**), corotoxigenin, securigenol, pachygenin, and strophanthidin derivatives and their bufadienolide counterparts such as 19-hydroxybufalin (**3**). It should be noted that applying the previously developed synthetic approaches[4] to such steroids (including our diastereoselective approach[5b] depicted in Figure 1B) would require incorporating a strategy for selective removal of the C11 alcohol in the presence of the C3, C14, C17, and C19 oxygenation as well as other functionalities. This task might be operationally challenging and would result in a significant increase in the overall number of steps. To circumvent

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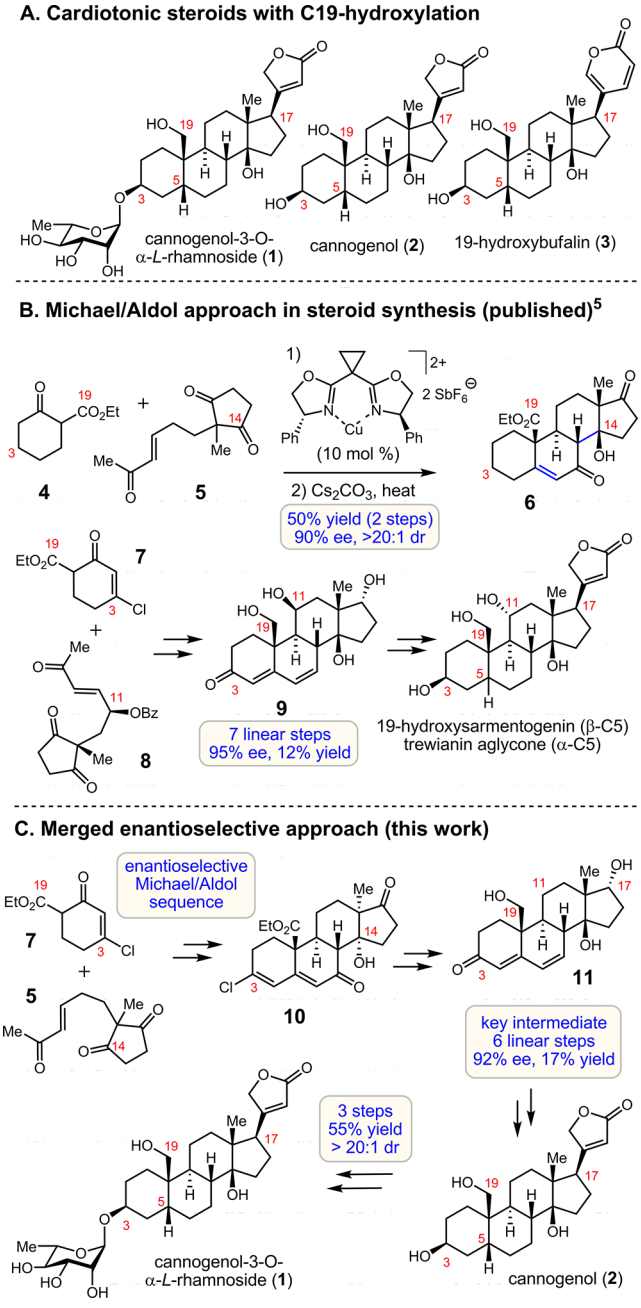
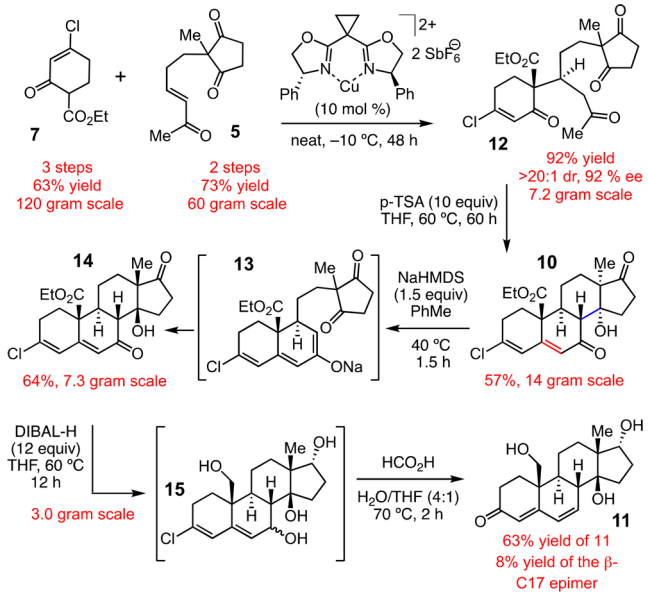


Figure 1. Prior and current synthetic approaches.

these problems, we pursued a more direct approach that is based on our enantioselective Cu(II)-catalyzed Michael reaction/aldolization of **7** and **5** resulting in steroid **10** (Figure 1C). This is the first example of using this strategy in the synthesis of natural cardenolides, and the formation of **10** is accomplished on decagram scale with excellent overall yield and selectivities.

Steroid **10** was then subjected to an epimerization/reductive transposition sequence to provide intermediate **11** lacking the C11 oxygenation. This expedient synthesis of **11** was accomplished in only 6 linear steps, 17% yield, and 92% ee on a 3 g scale. This key intermediate may be converted to various C19 oxygenated cardiotonic steroids, which was demonstrated by synthesizing cannogenol (**2**), a natural cardenolide with anticancer properties.[6] Finally, this manuscript describes a strategy to accomplish a regioselective introduction of sugar at the less reactive C3 position of **2** to provide natural cardiac glycoside cannogenol-3-*O*-α-L-rhamnoside (**1**),[7] an effective nanomolar growth inhibitor of several cancer cell lines.[6a,8] Our studies commenced with generating sufficient quantities of known precursors **5** and **7** (Scheme 1). Thus, β-ketoester **7** was

Scheme 1. Synthesis of Intermediate 11



prepared in three steps from 3-ethoxy-2-cyclohexenone (120 g scale) and enone **5** was synthesized in two steps from 2-methyl-1,3-cyclopentanedione (60 g scale). These substrates were subjected to asymmetric Michael reaction[5a] using a 2,2′-(cyclopropane-1,1-diyl)bis(4-phenyl-4,5-dihydrooxazole) ligand complexed with $Cu(SbF_6)_2$ as the catalyst (10 mol %) under neat conditions.[9] Gratifyingly, this transformation proceeded efficiently, and Michael adduct **12** was consistently generated on 7.2 g scale in 92% yield, >20:1 dr, and 92% ee. This compound was then subjected to aldolization with *p*-TSA, which resulted in steroid **10** with an unnatural α-C13/C14 configuration (57%, >20:1 dr, 14 g scale). Our prior studies on a related system containing C11 oxygenation[5c] indicated that such unnatural steroids could be epimerized under basic conditions to form the more stable natural β-configuration at the C13 and C14 stereocenters. Indeed, subjecting **10** to NaHMDS resulted in formation of the desired diastereomer **14** through the intermediacy of retro-aldol product **13** (64%, >20:1 dr; 7.3 g scale). Intermediate **14** was then treated with DIBAL-H (3 g scale), which led to **15**, which was stable at room temperature for up to 2 h. The tetraol **15** was not isolated, but rather the excess of DIBAL-H was quenched, and the crude mixture was heated at reflux in formic acid and 8:2 water/THF to accomplish transposition/vinyl chloride hydrolysis to produce a mixture of C17 epimers in 71% yield, 8:1 dr. This mixture was purified by SiO_2 column chromatography to afford α-C17 diastereomer **11** in 63% yield. This transformation allowed us to remove the unwanted oxygenation at C7 and introduced important oxygenation at C3 in a single step to set the proper steroidal framework mimicking the natural product. Thus, the key intermediate **11** was synthesized in 6 linear steps (9 overall steps) from commercially available building blocks in 17% overall yield and 92% ee.

With the key intermediate **11** in hand, we turned our attention to installation of the stereocenter at C5 and the butenolide ring at C17. Steroid **11** was subjected to hydrogenation with Pd/C in the

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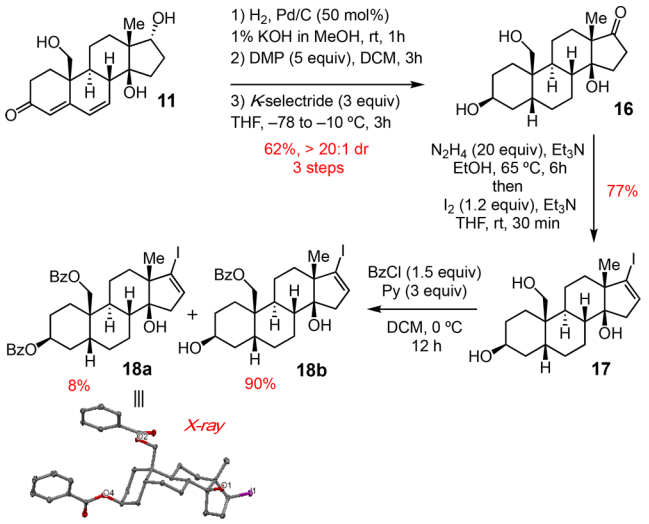
presence of 1% potassium hydroxide in methanol (Scheme 2). This C19 alcohol-directed hydrogenation resulted in the

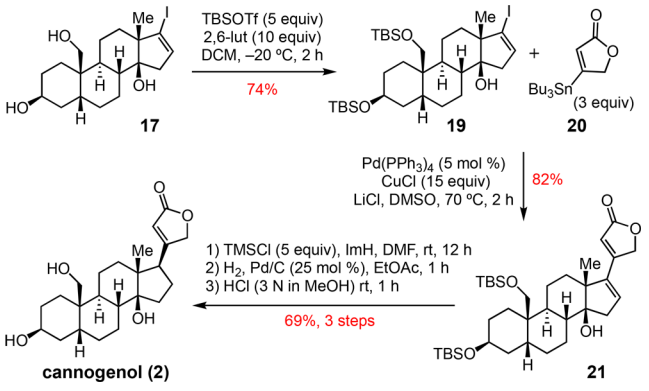
Scheme 2. Synthesis of Intermediate 17 and Confirmation of Its Absolute and Relative Configuration



exclusive formation of the β-C5 center. The subsequent global oxidation of the crude material using Dess-Martin periodinane (DMP) followed by the selective reduction of the C19 aldehyde and C3 ketone in the presence of the C17 ketone by a bulky K-selectride yielded **16** in 62% yield over three steps after a single purification at the end of the third step. The iodination of **16** under Barton's protocol[10] produced vinyl iodide **17** in 77% yield. Compound **17** was benzoylated to provide monobenzoate **18b** (90% yield) along with the crystalline *bis*-benzoate **18a** in 8% yield, the absolute and the relative configuration of which was confirmed by X-ray crystallographic analysis.

As the conditions for the deprotection of the C19 benzoate were not compatible with the butenolide functionality, **17** was subjected to TBS protection (Scheme 3) resulting in intermediate **19** in 74% yield.

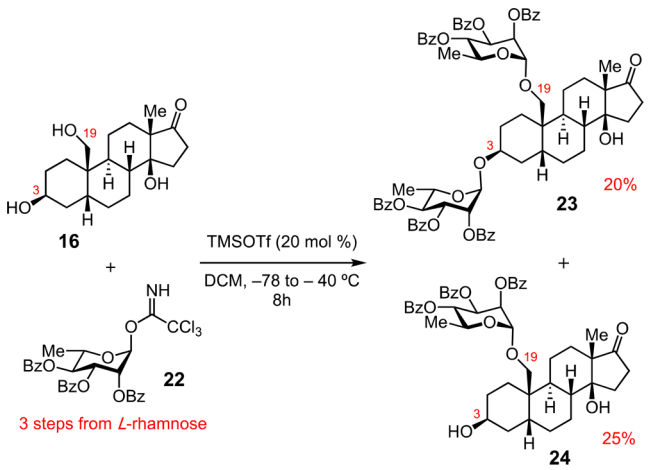
Scheme 3. Synthesis of Cannogenol from 17



This protection was necessary, as the direct Stille coupling of **17** and **20** was sluggish and resulted in lower yields. In contrast, the Stille coupling of **19** and commercially available stannylated butenolide **20** proceeded efficiently and resulted in steroid **21** in 82% yield. This product was elaborated to cannogenol (**2**) via a three-step sequence in 69% yield.[4f,h] This sequence involved TMS protection of the C14 tertiary alcohol, hydrogenation of the Δ^{16}-olefin, and global removal of the silyl protecting groups. The TMS protection of the C14 tertiary alcohol was required to achieve a steric bias for the subsequent hydrogenation to give exclusive β-C17, and the attempts to accomplish this protection prior to the Stille coupling reaction resulted in poor yields of the cross-coupled product.

Next, we investigated the possibility of adopting this route to the synthesis of cannogenol-3-*O*-α-L-rhamnoside (**1**). Our initial studies commenced with attempts to accomplish C3-selective glycosylation of triol **16** as a model substrate (Scheme 4).

Scheme 4. Initial Glycosylation Studies



Attempts to glycosylate **16** with trichloroacetimidate **22** available in three steps from L-rhamnose[4b,c,11] resulted in the equimolar mixture of products **23** and **24** formed in ~70% conversion. This result indicated that the C19 hydroxyl is more reactive than the secondary C3 alcohol.

Anticipating similar reactivity trends for cannogenol (**2**), our following efforts were focused on selectively protecting the C19 position of **2** (Scheme 5). Due to its higher reactivity, the C19 hydroxyl could be selectively protected as a *p*-bromobenzoate (**27**) or an acetate (**28**). These derivatives were glycosylated with trichloroacetimidate **22** using TMSOTf as a promoter to afford protected α-glycosides **27** (36% yield) and **28** (56% yield). These glycosylated steroids were subjected to ester deprotection under basic conditions; however, this step represented a significant challenge. The use of various basic conditions for ester hydrolysis (i.e., Na_2CO_3, K_2CO_3, NaOMe, LiOH, or NH_3) resulted in the deprotection of the benzoyl esters on the rhamnose moiety. However, the deprotection of the C19 ester was slow and proceeded with the formation of multiple side products due to concomitant opening and isomerization of butenolide. To address this problem, more labile C19 methoxyacetate **29** was prepared in 99% yield. This compound was subjected to TfOH-catalyzed glycosylation with **22**, which resulted in α-rhamnoside **30** in 81% yield (>20:1 dr). Compound **30** was subjected to ammonia (50% solution in methanol) to provide the desired cannogenol-3-*O*-α-L-rhamnoside (**1**) in 69% yield. The ^{1}H, ^{13}C NMR data and optical rotation data ($[\alpha]_D^{20} = -10.8$, $c = 0.147$ in MeOH, reported[7] $[\alpha]_D^{20} = -15.5$, $c = 0.55$ in MeOH) of the synthetic **1** were in good agreement with the corresponding data obtained for the natural sample of **1**.[6a,7,8]

In conclusion, a new asymmetric approach to cardenolides carrying the C19 oxygenation has been developed and applied to the synthesis of the natural products cannogenol (**2**) and

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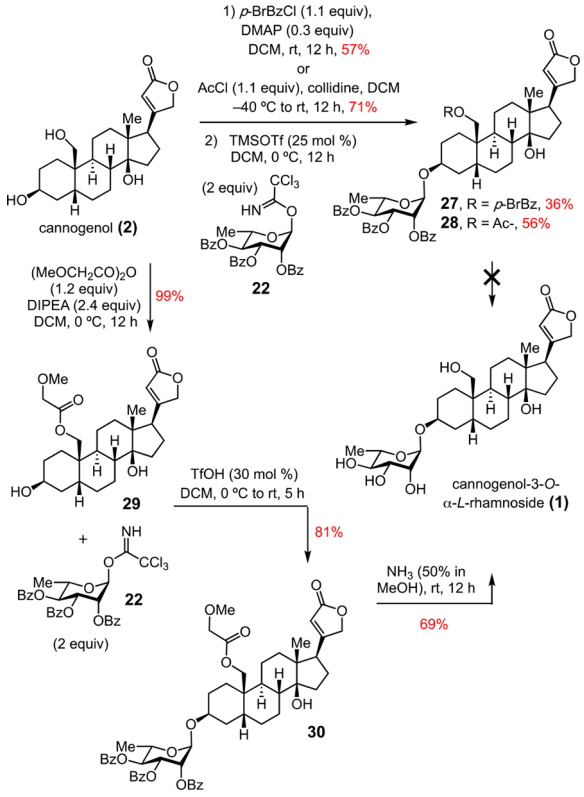
Scheme 5. Synthesis of Cannogenol-3-*O*-α-L-rhamnoside (1) from Cannogenol (2)



cannogenol-3-*O*-α-L-rhamnoside (**1**) possessing anticancer activity. This approach features 3 g scale enantioselective synthesis of the functionalized cardenolide core in 6 linear steps, 17% yield, and 92% ee involving an enantioselective Michael/tandem Aldol addition sequence established by our group earlier. This key intermediate could be elaborated to cardenolide cannogenol (**2**) in 9 steps, 20% yield. Cannogenol (**2**) contains multiple hydroxyl functionalities, and a strategy for the selective introduction of sugar moieties at the C3 position of **2** was developed and successfully applied to the formation of cannogenol-3-*O*-α-L-rhamnoside (**1**). The herein described strategies will expedite medicinal chemistry studies on C19-hydroxylated cardenolides related to cannogenol, and the exploration of **1**, **2**, and related analogs is the subject of ongoing investigation by our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03513.

Experimental procedures, ^{1}H and ^{13}C NMR spectra of compounds (PDF)

Accession Codes

CCDC 1585371 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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