

First Total Synthesis of Rhodexin A

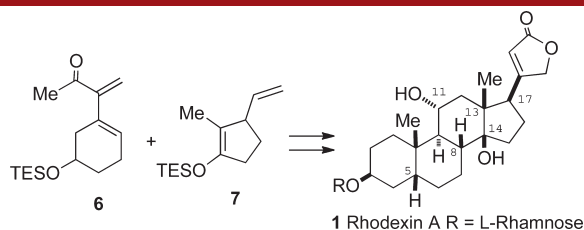
Michael E. Jung* and Dongwon Yoo

Department of Chemistry and Biochemistry, University of California, Los Angeles, 405
Hilgard Avenue, Los Angeles, California 90095, United States

jung@chem.ucla.edu

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ABSTRACT



An efficient total synthesis of rhodexin A (1) is reported. An initial inverse-electron-demand Diels–Alder reaction of the acyldiene 6 with the silyl enol ether 7 gave the cycloadduct 8 with the required 4 contiguous stereocenters in a single step. This compound was then transformed into the tetracyclic enone 16, which was converted to rhodexin A (1).

More than 200 natural cardiac glycosides have been isolated from a variety of plant sources. Many of these have shown potent cardiotonic activity,¹ including rhodexin A (1), the L-rhamnoside of sarmentogenin. This glycoside was isolated in 1951² from the leaves and roots of the Japanese evergreen *Rhodea japonica* and has been found in several other plant species as well. Besides being the only compound in its family to display a digitalis-like action in the cat heart,³ rhodexin A is also active against human leukemia K562 cells (IC₅₀ of 19 nM).⁴ Indeed, it is one of a series of cardiac glycosides that have potent antiproliferative activity, which has been attributed to their ability to inhibit synthesis of hypoxia inducible factor 1 (HIF-1α).⁵

However, rhodexin A differs from most common steroids in that its AB and CD rings are *cis* rather than *trans* fused, and it possesses a tertiary hydroxyl group at C₁₄ and a β-butenolide substituent at C₁₇ (Figure 1). Because of its unique stereochemistry and potent bioactivity, rhodexin A represents an attractive synthetic target. We report here an efficient total synthesis of rhodexin A (1).

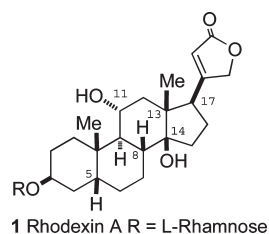


Figure 1

Our retrosynthesis involved the preparation of the BCD tricyclic system by an inverse-electron-demand Diels–Alder reaction that would set the four desired contiguous stereocenters of the natural product (C₈, C₁₃, C₁₄, and C₁₇) in a single step (Scheme 1). The inverse-electron-demand Diels–Alder reaction can be achieved by using the diene 2, which possesses the functionality required to elaborate the A ring onto the existing BCD tricyclic core, and a dienophile 3 that contains a functional group which could be

(1) For reviews, see: (a) Mehanna, A. S. *Foye's Principles of Medicinal Chemistry*, 6th ed.; Lemke, T. L., Williams, D. A., Eds.; Lippincott: Philadelphia, 2008; pp 698–721. (b) Somberg J. G. B.; Tepper, D. J. *Clin. Pharmacol.* **1985**, 484–489. (c) Haustein, K.-O. *Pharmacol. Ther.* **1982**, 18, 1–89.

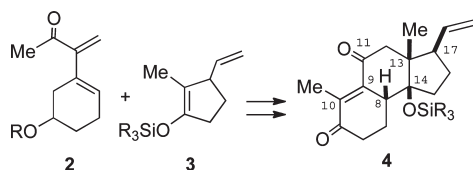
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Scheme 1



transformed to the butenolide moiety at a later stage of the synthesis.⁶ We anticipated that the cycloaddition would occur via the most favored *exo* transition state **A** in which the vinyl group ($R = \text{vinyl}$) is on the face opposite bond formation since the other *exo* transition state **B** has greater steric interaction (Figure 2). The *exo* structures should be favored over the *endo* **C** and **D**, since in the *endo* transition state placement of the methyl group and the silyl ether under the diene should lead to much greater steric hindrance than the opposite *exo* transition state, where the three methylenes of the cyclopentene lie under the diene.⁶

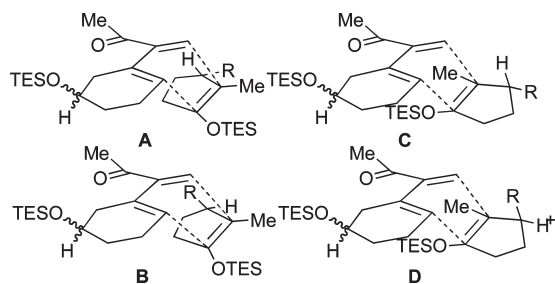


Figure 2

To test the key inverse-electron-demand Diels–Alder reaction, we prepared the desired diene **6** in a single step by treating the silyl-protected enynone **5** (made in two steps from the known enynol)⁷ under enyne metathesis conditions (Scheme 2). The vinyl silyl enol ether **7** was prepared in one step by the copper-catalyzed 1,4-addition of vinyl-lithium to the enone followed by trapping of the enolate in the presence of TESCl and HMPA.⁸ Reaction of the two components could be effected using several catalytic acid systems, e.g., 5:1 $\text{AlMe}_3/\text{AlBr}_3$,⁶ but we found that it was best carried out using 10 mol % of triflimide (TiF_2NH) as the Lewis acid in dichloromethane at -78°C for 5 min to afford the tricyclic system **8** in 86% yield as a 2:1 mixture of two diastereomers at the secondary silyl ether group.⁹

(6) For examples of sterically hindered inverse-electron-demand Diels–Alder reactions, see: (a) Jung, M. E.; Chu, H. V. *Org. Lett.* **2008**, *10*, 3647–3649. (b) Jung, M. E.; Ho, D.; Chu, H. V. *Org. Lett.* **2005**, *7*, 1649–1651. (c) Jung, M. E.; Davidov, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 4125–4128.

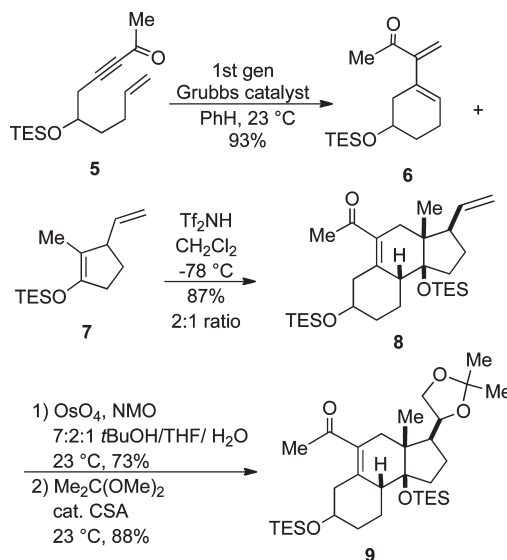
(7) Parsons, P. J.; Caddick, S. *Tetrahedron* **1994**, *50*, 13523–13532.

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Since that center would become a ketone later in the synthesis, this mixture was of no consequence. Dihydroxylation of the vinyl side chain and protection of the diol as the acetonide was accomplished to give **9**.

Scheme 2

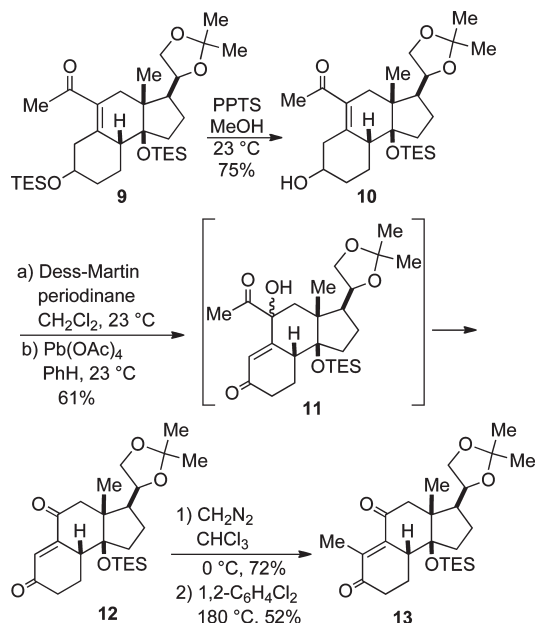


Installation of the oxygen atom at C_{11} followed our previous route, namely the very unusual triple oxidation with the Dess–Martin periodinane (DMP) of the homo-allylic alcohol **10**, prepared by selective mildly acidic hydrolysis of the less hindered silyl ether of **9** (Scheme 3). Presumably, oxidation to the enedione occurs, followed by α -hydroxylation of this very enolic species at C_{11} to give the hydroxy enedione **11**. This can then be oxidized with excess DMP, although we prefer to use lead tetraacetate for the final cleavage. In this way, the enedione **12** is isolated in 61% yield. The C_{10} methyl group was installed via the two-step sequence of the 1,3-dipolar cycloaddition of diazomethane to **12** to give the pyrazoline in 72% yield, followed by extrusion of nitrogen to afford the methyl enedione **13** in 52% yield.¹⁰

The functionalized tricycle **13** was converted into the tetracyclic enone **16** via an unusual annulation process (Scheme 4). Reductive alkylation of the enedione **13** using lithium in ammonia and trapping with allyl bromide gave the desired product **14** in 52% yield. The stereochemistry of **14** was assigned by proton NMR experiments and was confirmed by an X-ray analysis of a later intermediate. We were unable to trap the bis(enolate) produced in the reduction with any more functionalized allyl analogues,

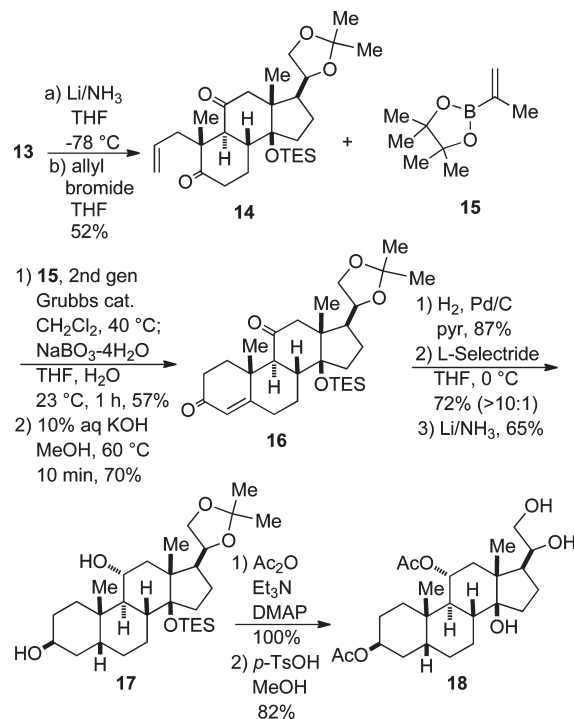
(10) (a) Nemoto, H.; Matsushashi, N.; Imaizumi, M.; Nagai, M.; Fukumoto, K. *J. Org. Chem.* **1990**, *55*, 5625–5631. (b) Nemoto, H.; Nagai, M.; Moizumi, M.; Kohzuki, K.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1639–1645. (c) Nemoto, H.; Nagai, M.; Moizumi, M.; Kohzuki, K.; Fukumoto, K.; Kametani, T. *Tetrahedron Lett.* **1988**, *29*, 4959–4962.

Scheme 3



although many were tried.¹¹ However, we succeeded in preparing the enone by a new route. Cross-metathesis of this alkene with the isopropenyl (pinacolato)boronate **15**,¹² prepared by reaction of isopropenylmagnesium bromide with trimethyl borate followed by treatment with acid and pinacol, using the Grubbs second-generation catalyst, afforded in 57% yield the substituted alkenyl boronate, which was directly oxidized with sodium perborate to give the diketone in 99% yield. Final base-catalyzed aldol condensation furnished the desired enone **16**. An X-ray crystal structure (Figure 3) confirmed the stereochemistry.¹³ As far as we know, this is the first time such a sequence has been used for an annulation process. Chemo- and stereoselective reduction of the enone **16** via catalytic hydrogenation using palladium on carbon in the presence

Scheme 4



of pyridine gave exclusively the desired product with the *cis* AB ring junction in 87% yield. Reduction of the C-3 ketone using L-Selectride gave in 72% yield the axial alcohol, and dissolving metal reduction of the C-11 ketone furnished in 65% yield the equatorial alcohol **17** (the stereochemistry of both was confirmed by NMR studies). Protection of the diol as the diacetate and acidic methanolysis of the acetonide gave the triol **18** in which the tertiary silyl ether also had been removed.

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(13) We thank Dr. Saeed Khan (UCLA) for the X-ray structural analysis.

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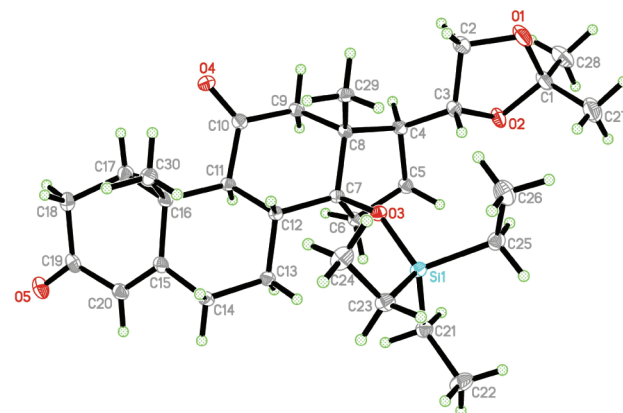
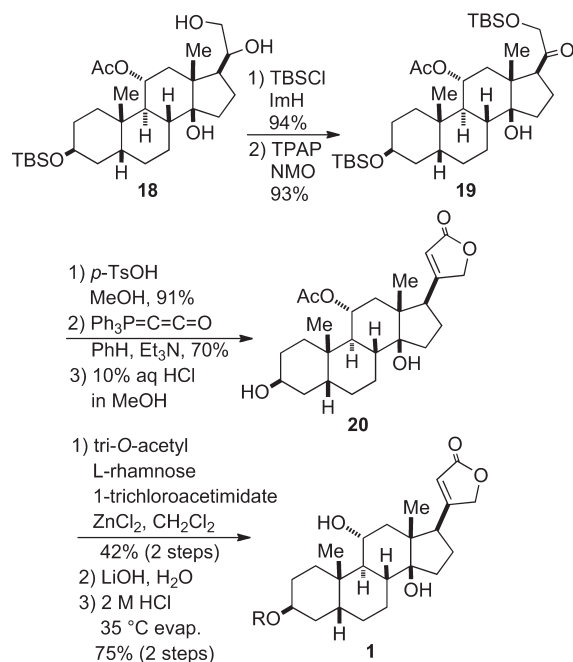


Figure 3

The final conversion of **18** to rhodexin A (**1**) required formation of the butenolide and attachment of the L-rhamnose (Scheme 5). Selective protection of the

Scheme 5



primary alcohol and oxidation gave the silyloxy ketone **19** in excellent yield. Mild acidic hydrolysis of the TBS ether (91% yield) followed by reaction with the Bestmann reagent, triphenylphosphoranylidene ketene, prepared in situ, provided the butenolide in 70% yield. Selective removal of the C-3 acetate in the presence of the C-11

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acetate and the butenolide was carried out with HCl in methanol to give the diol, sarmentogenin acetate, **20**, in good yield.¹⁴ Reaction of tri-*O*-acetyl L-rhamnose 1-trichloroacetimidate¹⁵ with the less hindered secondary alcohol of **20** using a standard protocol (ZnCl_2) followed by global removal of the acetates (aq LiOH) and recyclization of the hydroxy acid salt formed by opening of the butenolide by stirring with 2 M HCl afforded rhodexin A (**1**). The identity of our synthetic sample with natural rhodexin A was confirmed by comparison of the high-field ^1H and ^{13}C NMR spectra with those of the natural material.¹⁶

In summary, we have completed the first total synthesis of rhodexin A (**1**), a novel cardiac glycoside with potent antiproliferative activity. The key steps include an efficient inverse-electron-demand Diels–Alder reaction to generate the four contiguous stereocenters of the BCD ring system in a single step in excellent yield and high stereoselectivity, a novel annulation method for the formation of the A ring, and a novel cleavage–recyclization of the butenolide in the end game. Further methods for the synthesis of cardiac glycosides¹⁷ are underway and will be reported in due course.

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Supporting Information Available. Experimental procedures and proton and carbon NMR data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(16) We thank Professor Toshiya Masuda, Faculty of Integrated Arts and Sciences, University of Tokushima, for kindly providing both the spectra of rhodexin A and a small sample of the natural material.

(17) Recently, an excellent synthesis of a related steroid, ouabain, was reported using a Michael–aldol approach: Zhang, H.; Reddy, M. S.; Phoenix, S.; Deslongchamps, P. *Angew. Chem., Int. Ed.* **2008**, 47, 1272–1275.