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First Total Synthesis of Rhodexin A

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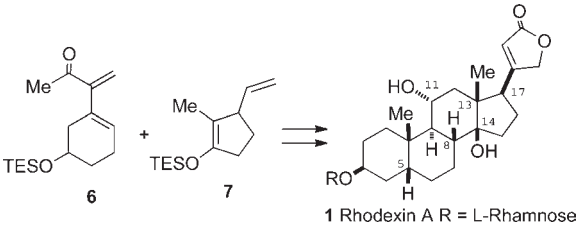
ABSTRACT



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 1951[2] 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 (IC_{50} 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 C_{14} and a β-butenolide substituent at C_{17} (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**).

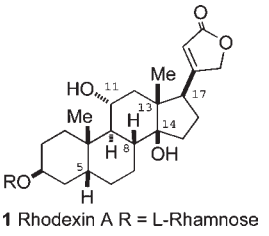


Figure 1

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 (C_8, C_{13}, C_{14}, and C_{17}) 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.

(2) Nawa, H. *Proc. Japan Acad.* **1951**, *27*, 436–440. The compound was originally spelled "rohdexin A" since it was isolated from *Rohdea japonica*, but that was later changed to the current spelling.

(3) Kikuchi, K.; Chen, K. K. *J. Pharmacol. Exp. Ther.* **1964**, *146*, 365–368.

(4) (a) Umebayashi, C.; Yamamoto, N.; Nakao, H.; Toi, Y.; Chikahisa-Muramatsu, L.; Kanemaru, K.; Masuda, T.; Oyama, Y. *Biol. Pharm. Bull.* **2003**, *26*, 627–630. (b) Masuda, T.; Oyama, Y.; Yamamoto, N.; Umebayashi, C.; Nakao, H.; Toi, Y.; Takeda, Y.; Nakamoto, K.; Kuninaga, H.; Nishizato, Y.; Nonaka, A. *Biosci. Biotechnol. Biochem.* **2003**, *67*, 1401–1404.

(5) (a) Lin, J.; Carducci, M. A. *Expert Opin. Invest. Drugs* **2009**, *18*, 241–243. (b) Lin, J.; Denmeade, S.; Carducci, M. A. *Curr. Cancer Drug Targets* **2009**, *9*, 881–887. (c) Newman, R. A.; Yang, P.; Pawlus, A. D.; Block, K. I. *Mol. Intervent.* **2008**, *8*, 36–49. (d) Langenhan, J. M.; Peteres, N. R.; Guzei, I. A.; Hoffmann, F. M.; Thorson, J. S. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 12305–12310.

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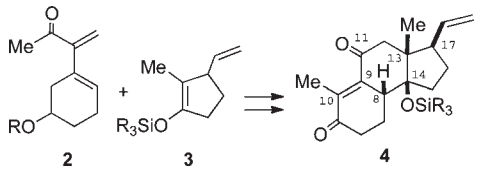
Scheme 1



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 = 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]

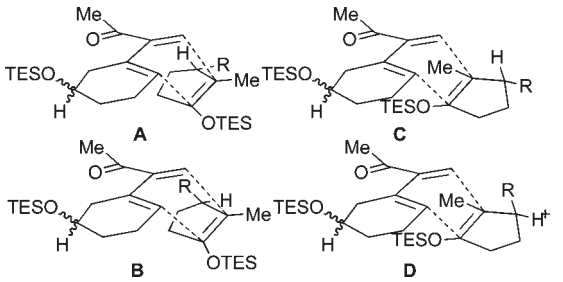
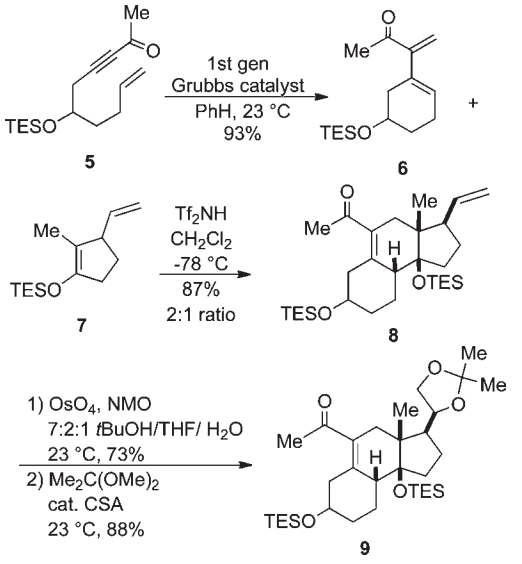


Figure 2

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 vinyllithium 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 $AlMe_3/AlBr_3$,[6] but we found that it was best carried out using 10 mol % of triflimide (Tf_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] 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 homoallylic 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 C11 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,

(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.

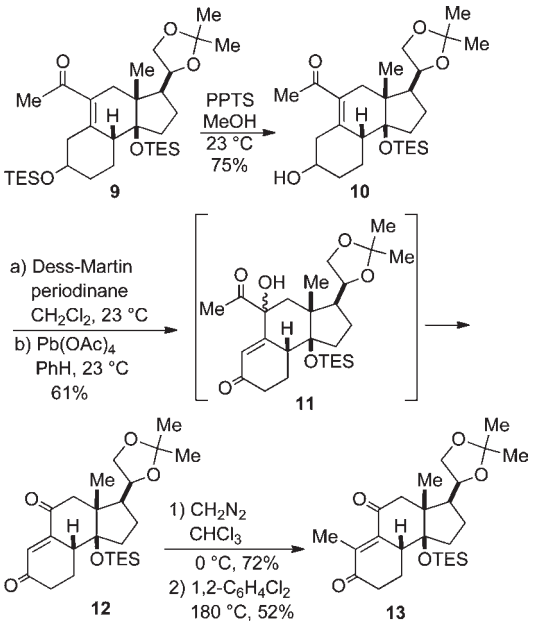
(7) Parsons, P. J.; Caddick, S. *Tetrahedron* **1994**, *50*, 13523–13532.

(8) Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1980**, *102*, 5253–5261.

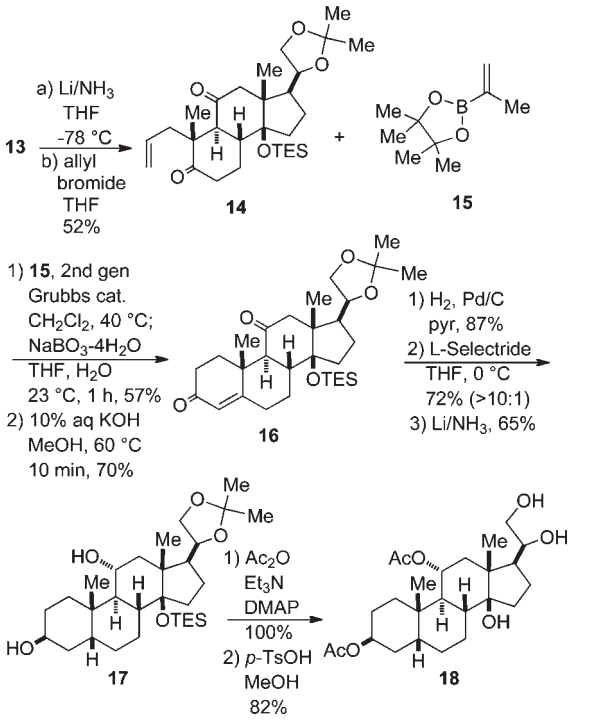
(9) Jung, M. E.; Ho, D. G. *Org. Lett.* **2007**, *9*, 461–463.

(10) (a) Nemoto, H.; Matsuhashi, 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



Scheme 4



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 isopropenylmagensium 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 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.

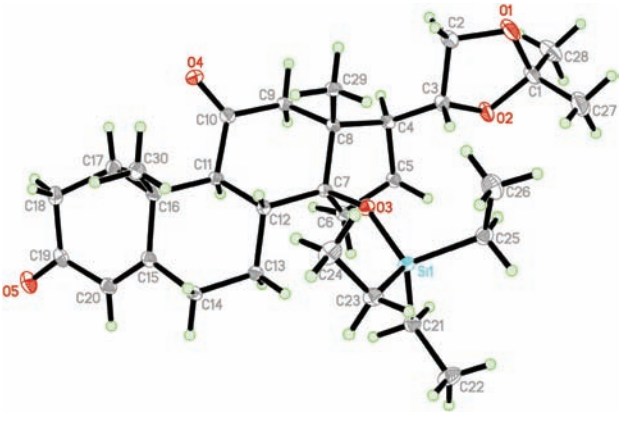


Figure 3

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

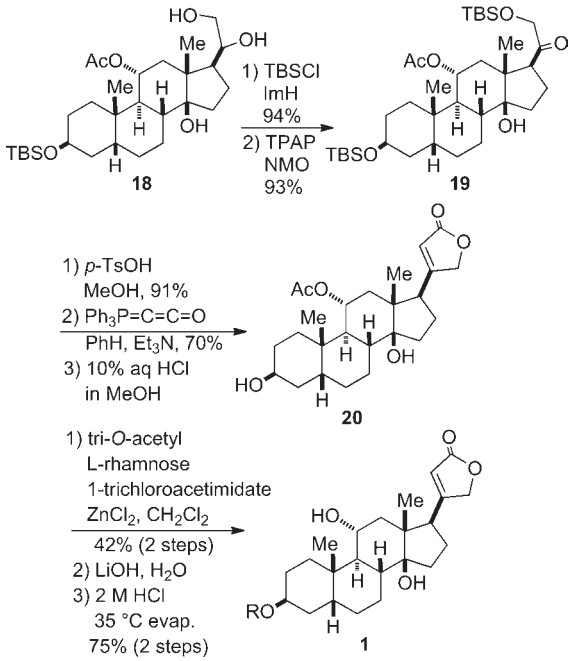
(11) (a) Singletary, J. A.; Lam, H.; Dudley, G. B. *J. Org. Chem.* **2005**, *70*, 739–741. (b) Snider, B. B.; Shi, B. *Tetrahedron Lett.* **2001**, *42*, 9123–9126. (c) Daniewski, A. R.; Piotrowska, E. *Liebigs Ann. Chem.* **1989**, 571–576. (d) Van Royen, L. A.; Mijngheer, R.; De Clercq, P. J. *Tetrahedron Lett.* **1983**, *24*, 3145–3148. (e) Stork, G.; Winkler, J. D.; Shiner, C. S. *J. Am. Chem. Soc.* **1982**, *104*, 3767–3768. (f) Stork, G.; Logusch, E. W. *J. Am. Chem. Soc.* **1980**, *102*, 1219–1220. (g) Stork, G.; Jung, M. E.; Colvin, E.; Noel, Y. *J. Am. Chem. Soc.* **1974**, *96*, 3684–3686. (h) Stork, G.; Jung, M. E. *J. Am. Chem. Soc.* **1974**, *96*, 3682–3684.

(12) (a) Zhao, Y.-J.; Loh, T.-P. *Org. Lett.* **2008**, *10*, 2143–2145. (b) Solorio, D. M.; Jennings, M. P. *J. Org. Chem.* **2007**, *72*, 6621–6623. (c) Yoo, K. S.; Yoon, C. H.; Jung, K. W. *J. Am. Chem. Soc.* **2006**, *128*, 16384–16393. (d) Morrill, C.; Funk, T. W.; Grubbs, R. H. *Tetrahedron Lett.* **2004**, *45*, 7733–7736. (e) Wu, B.; Liu, Q.; Sulikowski, G A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6673–6675. (f) Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3172–3174. (g) Fontani, P.; Carboni, B.; Vaultier, M.; Carrie, R. *Tetrahedron Lett.* **1989**, *30*, 4815–4818.

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

(14) For examples of such selective hydrolyses, see: (a) Yoshii, E.; Koizumi, T.; Ikeshima, H.; Ozaki, K.; Hayashi, I. *Chem. Pharm. Bull.* **1975**, *23*, 2496–2506. (b) Danieli, N.; Mazur, Y.; Sondheimer, F. *Tetrahedron* **1966**, *22*, 3189–3193. (c) Danieli, N.; Mazur, Y.; Sondheimer, F. *J. Am. Chem. Soc.* **1962**, *84*, 875–876. (d) Euw, J. v.; Reichstein, T. *Helv. Chim. Acta* **1952**, *35*, 1560–77.

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, triphenylphosphoranylideneketene, prepared in situ, provided the butenolide in 70% yield. Selective removal of the C-3 acetate in the presence of the C-11 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-trichloroacetimidate[15] 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 glycosides[17] 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.

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(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.