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# Preparation of a Functionalized Tetracyclic Intermediate for the Synthesis of Rhodexin A

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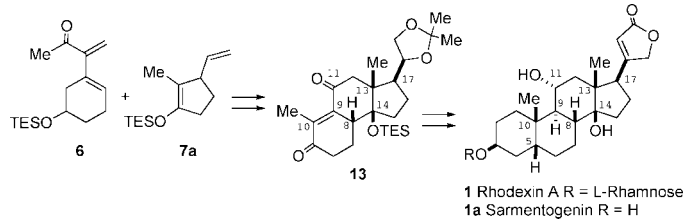
## ABSTRACT

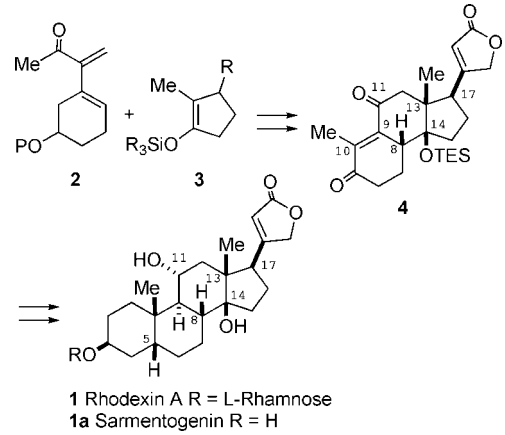



**An efficient synthesis of the tetracyclic steroid core, 19, of rhodexin A and sarmentogenin is reported. An initial inverse-electron-demand Diels−Alder reaction of the acyldiene 6 with the silyl enol ether 7a gave the cycloadduct 8 with the required four contiguous stereocenters in a single step. This compound was then transformed into the methylated enedione 13 which afforded after a reductive alkylation and annulation sequence the tetracycle 19.**

Rhodexin A **1**, the L-rhamnoside of sarmentogenin **1a**, is a cardiac glycoside that was isolated in 1951[1] from the leaves and roots of the evergreen *Rhodea japonica*, commonly used in traditional gardening and *ikebana*, flower arrangement, in Japan. The only compound in its family to display a digitalis-like action in the cat heart,[2] rhodexin A is also active against human leukemia K562 cells ($IC_{50}$ 19 nM).[3] Like all cardiac glycosides, 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 $\beta$-butenolide substituent at $C_{17}$. Due to its unique stereochemistry and potent bioactivity, rhodexin A represents an attractive synthetic target. We report here an efficient synthesis of the tetracyclic core of rhodexin.

Our synthetic strategy first 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). We anticipated that

**Scheme 1**




(1) Nawa, H. *Proc. Jpn. Acad.* **1951**, *27*, 436.
(2) Tawada, S. *Okinawa no Yahusou Hyakka*; Naha Press: Naha, Japan, 1988.
(3) Umebayashi, C.; Yamamoto, N.; Nakao, H.; Toi, Y.; Chikahisa-Muramatsu, L.; Kanemaru, K.; Masuda, T.; Oyama, Y. *Biol. Pharm. Bull.* **2003**, *26*, 627.

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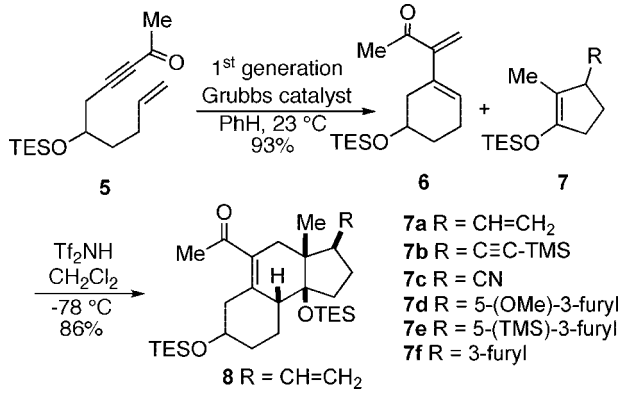
the cycloaddition would occur via the *exo* transition state since in the *endo* transition state, placement of the methyl group and the silyl ether under the diene should lead to much greater steric hindrance than the opposite *exo* transition state, where the three methylenes of the cyclopentene lie under the diene.[4] 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 transformed to the butenolide moiety at a later stage of the synthesis.[5]

To examine 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)[6] under enyne metathesis conditions (Scheme 2). A variety of silyl enol ether dienophiles were

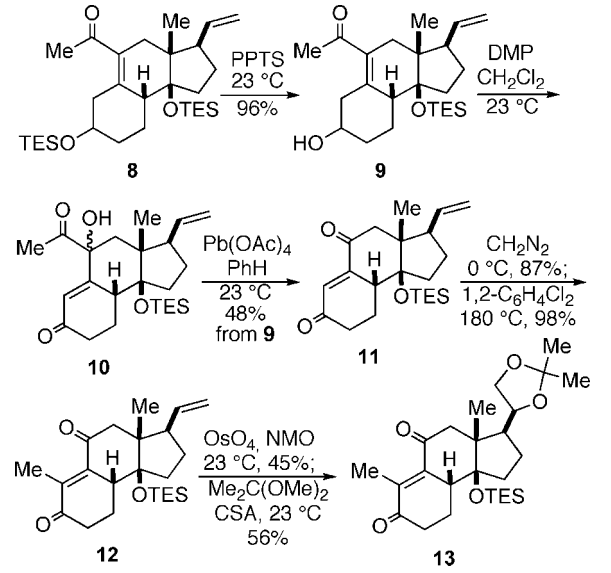
**Scheme 2**




synthesized containing a functional group that could eventually be transformed into the required butenolide moiety. However, most dienophiles (**7b**−**f**) were unstable when treated with Lewis acids for the Diels−Alder reaction. Fortunately, the desired *exo* cycloadduct **8** was obtained when the vinyl silyl enol ether **7a**[7] and the diene **6** were treated with various Lewis acids, such as $SnCl_4$, $MeAlCl_2$, or the mixed Lewis acid system $AlBr_3/AlMe_3$.[4] However, less than 50% of the cycloadduct was recovered when the above Lewis acids were used. The reaction was optimized by 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 mixture of two diastereomers at the secondary silyl ether group.[8] Since that center would become a ketone later in the synthesis, this mixture was of no consequence.

Attempts to install the oxygen atom at $C_{11}$ via a Baeyer−Villiger oxidation of the acetyl moiety in **8** were unsuccessful.[4a] These results prompted us to consider a new synthetic strategy, namely an oxidative deacetylation to afford the $C_{11}$ ketone functionality. Cleavage of the silyl group in **8** gave a mixture of secondary alcohols, which was oxidized with excess Dess−Martin periodinane (8 equiv) to give the enedione **11** in 48% yield (Scheme 3). Upon further

**Scheme 3**




investigation of this unusual oxidation process, we isolated, by using 3 equiv of the oxidant, the hydroxyl ketone intermediate **10**, which was oxidatively cleaved with additional Dess−Martin periodinane or lead tetraacetate to give the enedione **11** in 40% and 48% yield, respectively, over two steps. The installation of the $C_{10}$ methyl group was achieved through the two-step sequence of the 1,3-dipolar cycloaddition of diazomethane to **11**, followed by extrusion of nitrogen to afford the methyl enedione **12**.[9] The terminal vinyl group was dihydroxylated (to give a 7:1 diastereomeric ratio) and subsequently protected to give the acetonide **13**. Since the new chiral center is destroyed later in the synthesis, the diastereomeric mixture was not a problem.

With the functionalized tricyclic system in hand, we set about constructing the correct stereochemistry at both $C_9$ and $C_{10}$ utilizing a reductive alkylation process to provide the necessary functionality for the A-ring annulation sequence.[10,11] The reductive C-alkylation of the enedione **13**

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

(5) Recently a 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.

(6) Parsons, P. J.; Caddick, S. *Tetrahedron* **1994**, *50*, 13523.

(7) Compound **7a** was prepared by the modified procedure of Vollhardt, namely the copper-catalyzed 1,4-addition of vinyllithium in the presence of TESCl and HMPA. Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1980**, *102*, 5253.

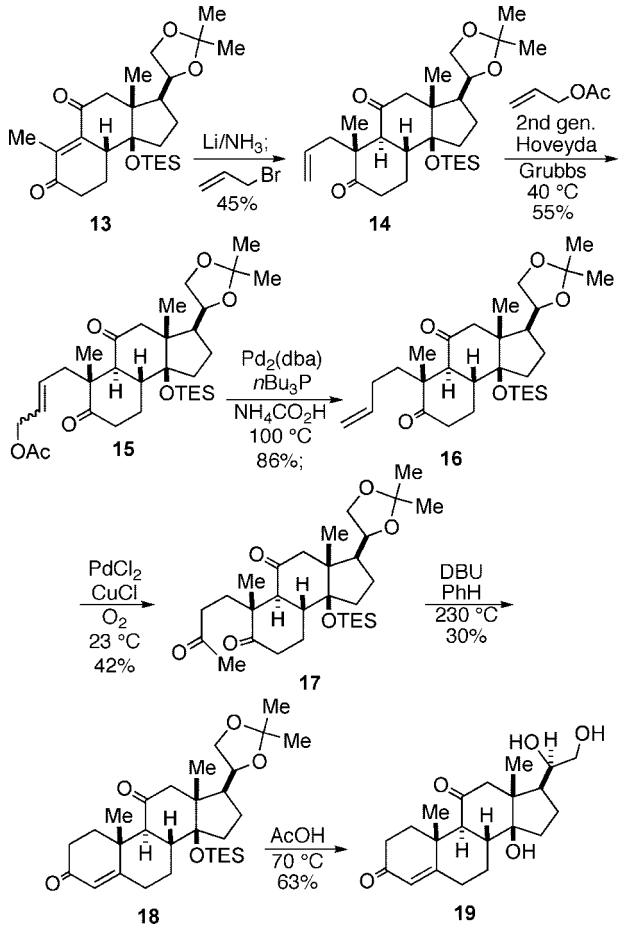
(8) Jung, M. E.; Ho, D. G. *Org. Lett.* **2007**, *9*, 461.

(9) For example, oxidation with *m*-CPBA, trifluoroperacetic acid, hydrogen peroxide, and bis(trimethylsilyl) peroxide in the presence of trimethylsilyl triflate gave only starting material.

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

afforded the desired diastereomer but in generally low yields using various well-known annulation reagents,[12] e.g., Wichterle reagents,[13] vinyl silanes,[14] etc. In addition, various Robinson annulation methods[12] on the saturated dione formed from **13** also failed. However, monoalkylation of the dienolate formed by reduction of the enedione **13** with lithium metal in liquid ammonia and THF with 3 equiv of allyl bromide yielded the desired alkylated product **14** in 45% yield (Scheme 4).

**Scheme 4**




Installation of the required additional carbon and functionality for the A-ring annulation by hydroboration of the terminal alkene was next attempted but proved unsuccessful. Extension of the carbon chain by one carbon was achieved using cross-metathesis with **14**. After attempts to use allyltrimethylsilane, isopropenyl acetate, or isopropenyl silyl ether were unsuccessful, we carried out the cross metathesis of the alkylated product **14** with allyl acetate using the second-generation Hoveyda−Grubbs catalyst[15] in dichloromethane at 40 °C for 48 h to yield the allylic acetate **15** as a mixture of *E* and *Z* stereoisomers. This allylic acetate **15** was then subjected to palladium-catalyzed hydrogenolysis[16] with rearrangement to yield the terminal alkene **16** in 86% yield. A Wacker oxidation was performed to generate the desired methyl ketone **17**. An intramolecular aldol reaction of the methyl ketone with 10 equiv of DBU in degassed benzene at 230 °C for 5 h furnished the tetracyclic steroid core **18**.[17] Finally, global deprotection gave the tetracyclic ring system of rhodexin A, **19**. The stereochemistry was assigned based on extensive high-field NMR data and was confirmed by a high-resolution X-ray crystal structure of **19** (Figure 1).[18]

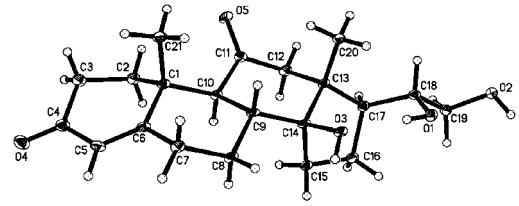



**Figure 1.** X-ray structure of triol **19**.

In summary, we have illustrated an efficient method for the synthesis of the BCD ring system of the steroid nucleus from an initial inverse-electron-demand Diels−Alder reaction which proceeded in excellent yield and high stereoselectivity to generate the four contiguous stereocenters in a single step. Furthermore, a reductive alkylation sequence provided the correct stereocenters at $C_9$ and $C_{10}$, leading to the formation of the steroid core **19**. The synthesis of rhodexin A **1** and new tricyclic BCD ring analogues will be reported in due course.

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**Supporting Information Available:** Experimental procedures and characterization for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL801426Z

(11) (a) Stork, G.; Logusch, E. W. *J. Am. Chem. Soc.* **1980**, *102*, 1219. (b) Stork, G.; Winkler, J. D.; Shiner, C. S. *J. Am. Chem. Soc.* **1982**, *104*, 3767. (c) Daniewski, A. R.; Piotrowska, E. *Liebigs Ann. Chem.* **1989**, 571.

(12) For reviews of annulation, see: (a) Jung, M. E. *Tetrahedron* **1976**, *32*, 3. (b) Gawley, R. E. *Synthesis* **1976**, 777.

(13) Van Royen, L. A.; Mijngheer, R.; De Clercq, P. J. *Tetrahedron Lett.* **1983**, *24*, 3145. See also refs 10b, c and 11b.

(14) (a) Stork, G.; Jung, M. E. *J. Am. Chem. Soc.* **1974**, *96*, 3682. (b) Stork, G.; Jung, M. E.; Colvin, E.; Noel, Y. *J. Am. Chem. Soc.* **1974**, *96*, 3684. (c) Snider, B. B.; Shi, B. *Tetrahedron Lett.* **2001**, *42*, 9123. (d) Singletary, J. A.; Lam, H.; Dudley, G. B. *J. Org. Chem.* **2005**, *70*, 739.

(15) Garber, S.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

(16) Tsuji, J.; Shimizu, I.; Minami, I. *Chem. Lett.* **1984**, 1017.

(17) Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1989**, *111*, 6257.

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