JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

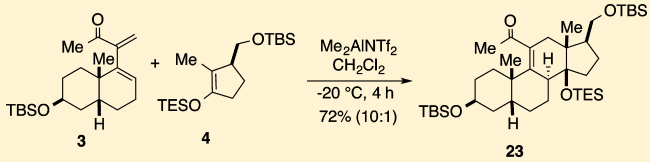
# Studies Toward the Enantiospecific Total Synthesis of Rhodexin A

Michael E. Jung* and Mikhail Guzaev

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, United States

Supporting Information

**ABSTRACT:** Studies toward the enantiospecific total synthesis of rhodexin A via a very hindered inverse electron demand Diels–Alder reaction are described. The C8-diastereomer of the fully elaborated tetracyclic core of rhodexin A, **23**, was prepared in good yield and excellent selectivity using as the key step the stepwise Diels–Alder reaction of the very hindered dienone **3** and the silyl enol ether **4** catalyzed by the very strong Lewis acid, dimethylaluminum triflimide.




## INTRODUCTION AND BACKGROUND

Cardiac glycosides are an abundant and diverse class of natural products isolated from a range of plant sources. Cardiotonic activity is a characteristic attribute of this class of compounds,[1] which includes rhodexin A (**1**), the L-rhamnoside of sarmentogenin (Figure 1). First isolated in 1951 from the leaves and roots of *Rohdea Japonica*, rhodexin A is also very active against human leukemia K562 cells ($IC_{50}$ of 19 nM).[2] The antiproliferative activity of this and other cardiac glycosides has been attributed to inhibition of the synthesis of hypoxia-inducible factor 1 (HIF-1$\alpha$).[3] In addition to its potent biological activity, rhodexin A is distinguished by its unusual geometry at the AB and CD ring junctures, displaying a cis rather than a trans fusion, a tertiary hydroxyl group at $C_{14}$, and a $\beta$-butenolide moiety at $C_{17}$. The appealing bioactivity of rhodexin A and its interesting set of synthetic challenges prompted our interest in pursuing an efficient and enantioselective total synthesis of rhodexin A. Our group has successfully completed a racemic synthesis of rhodexin A,[4] and a number of recent syntheses and synthetic work highlight fascinating chemistry in the area of complex steroids.[5]

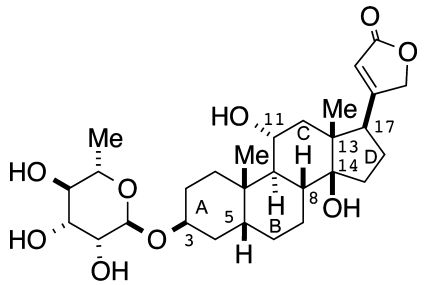



**Figure 1.** Structure of Rhodexin A.

In our retrosynthetic planning, we envisioned the butenolide moiety and C11 hydroxyl group being added late in the synthesis, utilizing the tetracyclic enone **2** (Scheme 1). An inverse electron demand Diels–Alder cycloaddition would install the three contiguous stereocenters at C8, C13, and C14, forming the steroid core of the molecule via reaction of the dienone **3** and the silyl enol ether **4** by a mechanism that is essentially a Mukaiyama Michael reaction, followed by a Mukaiyama aldol process. The success of the cycloaddition hinged on the steric encumbrance of the silyl ether and methyl group of the dienophile **4**, imparting exo selectivity, while the angular methyl group of dienone **3** would provide the required facial selectivity bias via steric hindrance on the top face of the molecule. Elaboration of the optically pure Wieland–Miescher ketone **5** and ring contraction of optically pure *S*-(+)-carvone **6** were identified as efficient and expedient methods for the preparation of the optically pure starting materials.

We report herein the efficient preparation of the C8 diastereomer **23** of the fully functionalized tetracyclic core of rhodexin A **1**, beginning with the readily available starting materials **5** and **6** and utilizing a very hindered stepwise Diels–Alder reaction.

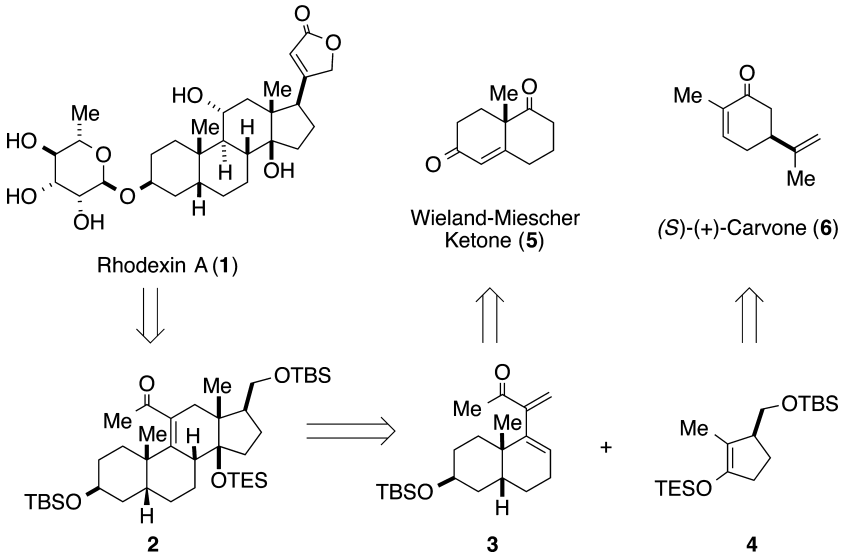
## RESULTS AND DISCUSSION

Conversion of the Wieland–Miescher ketone **5** into the dienone **3** began with the regioselective protection of the B ring ketone as the ketal **7**, using an exchange procedure with the ketal of ethyl methyl ketone.[6] Catalytic hydrogenation with palladium on carbon gave a 10:1 mixture of chromatographically separable diastereoisomers with the expected *cis*-decalin predominating.[7] Subsequent dissolving metal reduction established the desired stereochemistry of the A ring hydroxyl group to give, after acidic hydrolysis of the ketal, the equatorial alcohol **8** in 57% isolated yield over the three operations, two reductions and hydrolysis.[8] It is worth noting that the conformation of this *cis*-decalin unit (and the other *cis*-decalins of this entire scheme) prefers the conformation shown in **A**, since the proton $\alpha$ to the oxygen (Ha) appears as a pentet with small couplings (or as a broad signal without the expected

**Received:** May 17, 2013
**Published:** July 8, 2013

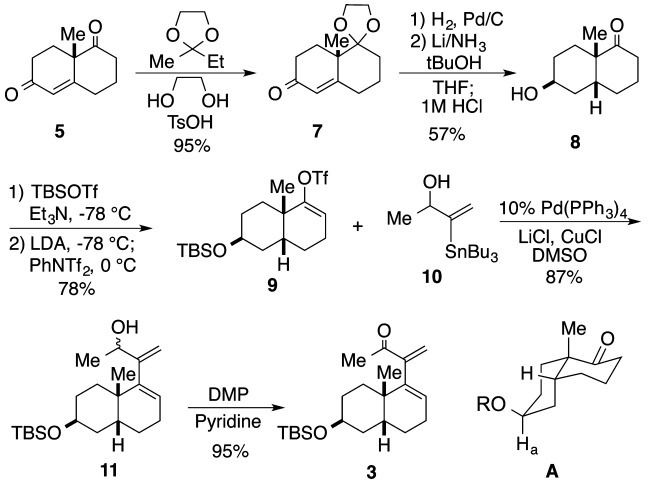
   dx.doi.org/10.1021/jo400909t | J. Org. Chem. 2013, 78, 7518–7526

**Scheme 1. Retrosynthetic Analysis of Rhodexin A**



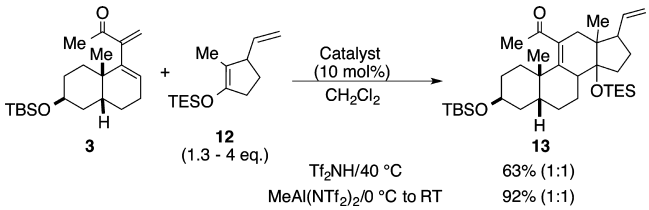

axial−axial coupling) and is, therefore, in the equatorial position. Protection of the hydroxyl group of **8** as the *tert*-butyldimethylsilyl (TBS) ether, followed by strong-base promoted enolization and trapping with *N*-phenyltriflimide ($PhNTf_2$), afforded the vinyl triflate **9** in good yield. Stille coupling of **9** with the $\alpha$-hydroxyethyl vinyl stannane **10** using the copper chloride/lithium chloride procedure[9] generated the allylic alcohol **11** in excellent yield. Finally, Dess−Martin periodinane (DMP) oxidation of the allylic alcohol in the presence of pyridine afforded the desired dienone **3**, completing the synthesis of the desired dienone fragment for the stepwise Diels−Alder reaction (Scheme 2).[10]

**Scheme 2. Synthesis of Dienone 3 from Wieland−Miescher Ketone 5**




With the completion of the synthesis of the AB ring fragment of the molecule, we decided to first study the stepwise Diels−Alder reaction of **3** with a racemic enol ether since this dienone **3** is extremely hindered and may have resulted in no cycloaddition. The quaternary center adjacent to the dienone unit would almost certainly require the diene to be non-coplanar, thereby eliminating the chance for a concerted Diels−Alder cycloaddition. However, we have already shown[11] that normal electron demand cycloadditions of 2-silyloxydienes and enones are indeed stepwise, being a Mukaiyama Michael process,[12] followed by intramolecular trapping (essentially a vinylogous Mukaiyama Michael process). We showed the nonconcerted nature of this reaction in hindered systems by isolating the initial Mukaiyama Michael adduct and showing that it could be converted on further reaction to the cyclo-adduct.[11] In the case of the dienone **3** and a silyl enol ether dienophile, the process is a stepwise Mukaiyama Michael reaction, followed by a vinylogous Mukaiyama aldol reaction at a very hindered center. Thus, we prepared the known racemic silyl enol ether **12**[4,13] in order to test the viability of the cycloaddition (Scheme 3). A number of conventional Lewis

**Scheme 3. Stepwise Diels−Alder Reaction of Dienone 3 with Silyl Enol Ether 12**




acids, including $SnCl_4$, $TiCl_4$, $BF_3{\cdot}OEt_2$, and $EtAlCl_2$, did not result in constructive catalysis. The mixed Lewis acid system, $AlMe_3/AlBr_3$, enjoyed some success, but was restricted by low yields.[14] Triflimide catalysis,[11] however, proved successful at higher temperatures, giving a 63% yield of **13**. However, in this very hindered system, $MeAl(NTf_2)_2$ was found to be the optimal catalyst, affording a 92% yield of the cycloaddition product **13**, as a 1:1 mixture of two diastereomers.[15,16] The reaction proceeded well with 1.3 equiv of the silyl enol ether **12**. A large excess of the dienophile was employed in the hope that resolution of the achiral enol might occur; however, no effect on the diastereoselectivity was observed. The possibility of preparing the silyl enol ether **12** in an enantioselective manner was briefly explored. However, a number of strategies, including rhodium-catalyzed enantioselective conjugate additions and cycloisomerization methods, failed to afford the desired compound.[17]


dx.doi.org/10.1021/jo400909t | J. Org. Chem. 2013, 78, 7518−7526

In the light of the diastereomeric ratio induced by an achiral dienophile, we considered using the known[18] pure silyloxy enone enantiomer **14** as the optically pure building block (Scheme 4). We anticipated that stereoselective conjugate addition and trapping with methyl iodide would afford the enone **15**. To avoid problems with alkene migration, as well as for greater overall synthetic convergence, we decided to employ an acetonide moiety as the protected eventual side chain in the design of dienophile **16**. Initially, we attempted the synthesis using the racemic compound **14**. Zinc-mediated conjugate addition of a vinyl organometallic to **14** and subsequent trapping with methyl iodide afforded predominately the all-trans isomer **15** as expected[19] (Scheme 5). Dihydroxylation of the alkene yielded the diol **17** as a 3:2 diastereomeric mixture of isomers at the newly formed stereocenter.[20] Acid-catalyzed elimination of the $\beta$-silyloxy group gave the enone, which was hydrogenated, and then the diol was protected with dimethoxypropane to afford the acetonide **18** in 46% over three steps. Silylation of this ketone with triethylsilyl triflate (TESOTf) and triethylamine resulted, unexpectedly,[21] in the less substituted silyl enol ether **19** in good yield. The alkene was migrated into the more substituted position using Wilkinson's catalyst[22] in chloroform to form the desired dienophile **16** in 65% yield.

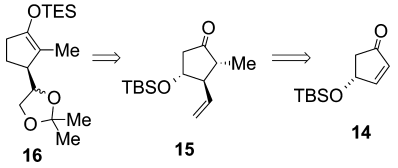
With the racemic dienophile **16** in hand, we next attempted its stepwise Diels–Alder reaction with dienone **3** using $Me_2AlNTf_2$ and $MeAl(NTf_2)_2$ catalysis. However, the reactions were unsuccessful (Scheme 6). Although both substrates were stable to the reaction conditions, no product was observed even with extended reaction times. We surmised that the acetonide competitively chelates the Lewis acid, impeding the reaction.[23] Modifications of the dienophile **16** were, therefore, considered. In an effort to diminish the chelating ability of the vicinal diol of **16**, bulkier protecting groups were investigated. Exposure of compound **18** to TBSOTf resulted in protection of the primary alcohol only, leaving the secondary alcohol exposed. Reaction with di-*t*-butylsilyl ditriflate[24] to form the bridged silyl ether resulted in prohibitively low yields. Because of the poor compatibility of the protected diol moiety with the desired transformations, an alternative dienophile substrate was considered.

In choosing a suitable dienophile, we were keenly aware of the importance of a convenient source of chirality. The known ring contraction chemistry of carvone[25] allowed us to prepare a potential dienophile substrate incapable of significant chelation from (*S*)-(+)-carvone, **6**. The established preparation of the silyl enol ether **22** was accomplished in 11 steps and 10% overall yield from (*S*)-(+)-carvone **6** (Scheme 7). The dienophile **22** was reacted with the dienone **3**; however, crude $^{13}C$ NMR studies indicated the substantial presence of a diketone byproduct, presumably due to the poor stability of the trimethylsilyl enol ether to the reaction conditions and hydrolysis of the initial Mukaiyama–Michael adduct with little net cycloaddition. A more robust version of this dienophile was consequently required.

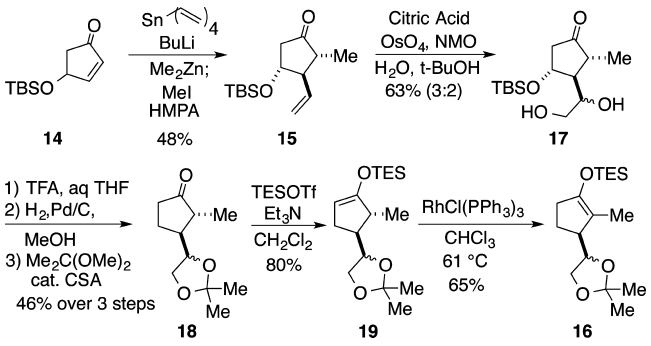
Exposing the silyl enol ether **22** to methyllithium in glyme gave the lithium enolate, which was trapped with triethylsilyl chloride to form the more stable dienophile **4**.[26] Finally, reaction of the dienone **3** and dienophile **4** catalyzed by 10 mol % $Me_2AlNTf_2$ at −20 °C for 4 h yielded the cycloadducts **23** and **24** in 72% yield as a 10:1 mixture of chromatographically separable diastereomers (Scheme 8).

To confirm the stereochemistry of the cycloadducts, formation of crystalline derivatives was attempted. Unfortunately, the major diastereomer **23** failed to yield suitable crystals, despite full deprotection and attempts at further derivatization as the dinitrophenyl hydrazone, *p*-bromoacetate, or *t*-butyl carbamate. The minor diastereomer **24** gave the crystalline triol **25** upon acid-catalyzed global deprotection (Scheme 9). Interestingly, the X-ray structure[27] (Figure 2)

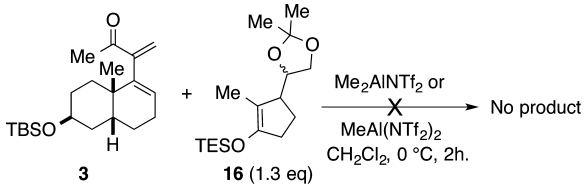
**Scheme 4. Retrosynthesis of Silyl Enol Ether Acetonide 16**



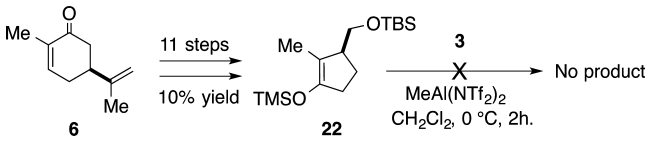

**Scheme 5. Synthesis of Silyl Enol Ether Acetonide 16**



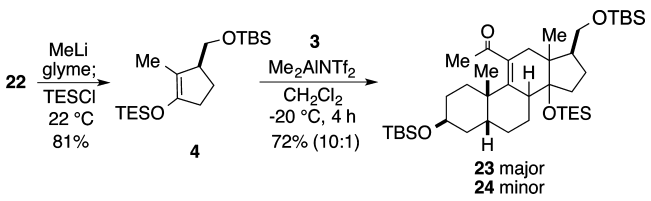

**Scheme 6. Attempted Stepwise Diels–Alder Reaction of 3 and 16**




**Scheme 7. Synthesis of Silyl Enol Ether Dienophile 22 from 6**



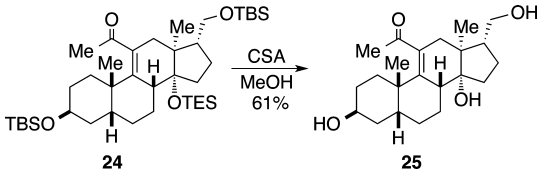

**Scheme 8. Successful Stepwise Diels–Alder Reaction of 4 and 3**





dx.doi.org/10.1021/jo400909t | J. Org. Chem. 2013, 78, 7518–7526

**Scheme 9. Global Deprotection of Minor Diastereomer 24 to give Crystalline Triol 25**



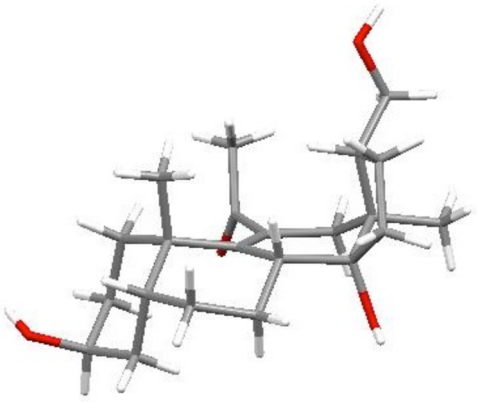
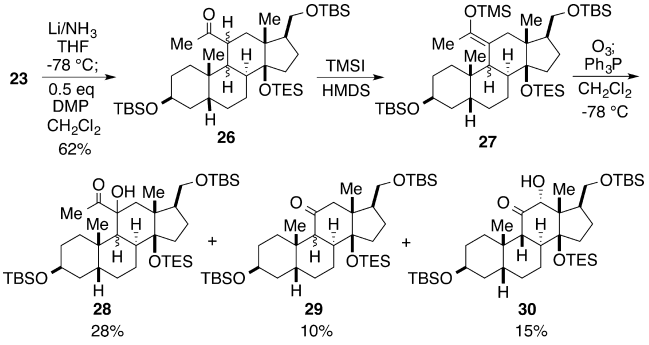



**Figure 2.** X-ray Structure of Triol **25**.

showed that compound **25** was the product of cycloaddition with the enantiomer of the dienophile **4**, which was most likely generated during the ring contraction of carvone, a known process.[28] Unable to determine the structure of the major diastereomer, we continued the synthesis in hopes of obtaining a crystalline intermediate. Dissolving metal reduction of the tetracycle **23** yielded a mixture of the ketone and a variety of diastereomers of over-reduced alcohol products (Scheme 10).

**Scheme 10. Conversion of Major Diastereomer 23 to the Crystalline Acyloin 30**




Upon exposure of the crude reaction material to Dess–Martin periodinane (DMP), the ketone **26** was isolated as a mixture of diastereomers in 62% overall yield. Formation of the more substituted silyl enol ether **27** proceeded in the presence of trimethylsilyl iodide and HMDS.[29] This compound proved unstable to silica gel chromatography and was used without purification in the next reaction. It is interesting to note that enolization with trimethylsilyl triflate and base yielded primarily the less substituted silyl enol ether. Ozonolysis of the silyl enol ether **27** resulted in a mixture of products, the major one being the acyloin **28**, although some of the desired ketone **29** was obtained as well.[30] Surprisingly, the crystalline acyloin **30** was also formed in the course of the reaction, thereby allowing analysis of the stereochemistry of the tetracyclic core via X-ray crystallography[27] (Figure 3). The mechanism of this oxidation of **27** to give **30** still remains unclear.

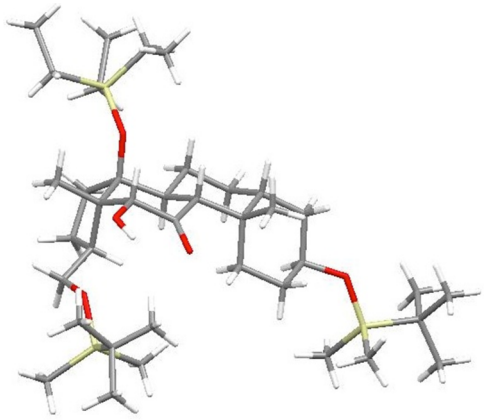


**Figure 3.** X-ray Structure of Acyloin **30**.

Upon examination of the structure of **30**, it became clear that the key Diels–Alder cycloaddition resulted in the formation of undesired stereochemistry at C8 at the BC ring juncture. Contrary to our proposal, the angular methyl at the AB ring juncture appeared to have offered insufficient steric bias to block the undesired facial approach. Thus, while the silyloxymethyl group afforded the correct facial attack on the silyl enol ether of **4**, the major direction of facial attack on the dienone **3** was opposite of that required for the correct stereochemistry at C8. This lack of selectivity may be due to the known stepwise nature of cycloadditions of such silyl enol ethers and dienones, enabling an unexpected set of transition-state geometries. Close examination of the two possible diastereomeric transition states for the second reaction, the Mukaiyama aldol process, provides good support for the observed results. In the transition state **31A**, the cyclopentanone carbonyl group can approach the vinylogous silyl enol ether carbon on the top face without significant steric hindrance, thereby leading to the observed product **23**. However, in transition state **31B**, approach of the cyclopentanone carbonyl on the bottom face of the vinylogous silyl enol ether carbon encounters significant steric hindrance due to strong nonbonded interactions of the methylene groups of the A ring with the cyclopentane ring system, thereby greatly disfavoring the formation of the product with the desired C8 hydrogen stereochemistry **32** (Scheme 11).

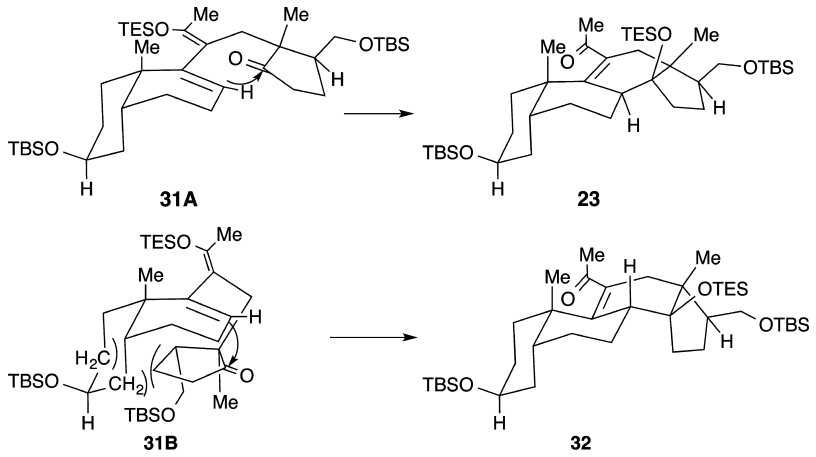
Since the proton at C9 could be easily equilibrated via treatment with base, the intermediate **23** could serve as a precursor to rhodexin A if the stereochemistry of the proton at C8 could be inverted. We attempted to remove this proton via $\gamma$-deprotonation of the enone of the cycloadduct **23** but met with no success since this very hindered substrate proved resistant to epimerization. Further attempts to correct the C8 stereochemistry are ongoing.

## ■ CONCLUSION

In summary, the assembly of the tetracyclic core of rhodexin A (**1**) via a very hindered inverse electron demand Diels–Alder reaction, catalyzed by the novel aluminum triflimide complex, $Me_2AlNTf_2$, was achieved. Further elaboration of the tetracyclic core and X-ray analysis revealed that the dienophile approach


dx.doi.org/10.1021/jo400909t | J. Org. Chem. 2013, 78, 7518–7526

**Scheme 11. Diastereomeric Transition States for Mukaiyama Aldol Process**




proceeds with undesirable facial selectivity, resulting in the C8 diastereomer of the rhodexin A core. Studies are currently underway to change the geometry at that diastereomeric center.

## EXPERIMENTAL SECTION

**General.** All reactions were carried out under an argon atmosphere unless otherwise specified. Tetrahydrofuran (THF), diethyl ether, toluene, and benzene were distilled from benzoquinone ketyl radical under an argon atmosphere. Dichloromethane (DCM), triethylamine (TEA), and diisopropylethylamine (DIPEA) were distilled from calcium hydride under an argon atmosphere. Triflimide ($Tf_2NH$) of 98% purity was weighed out in a nitrogen-filled glovebox and used as a 0.1 M solution in DCM. All other solvents or reagents were purified according to literature procedures. $^1$H NMR spectra were recorded at 400 and 500 MHz and are reported relative to deuterated solvent signals. Data for $^1$H NMR spectra are reported as follows: chemical shift ($\delta$ ppm), multiplicity, coupling constant (Hz), and integration. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. $^{13}$C NMR spectra were recorded at 100 and 125 MHz. Data for $^{13}$C NMR spectra are reported in terms of chemical shift. The chemical shifts are reported in parts per million (ppm, $\delta$). All Fourier transform infrared (FTIR) samples were prepared as thin films on NaCl plates, and spectra were recorded on a spectrometer and are reported in terms of frequency of absorption ($cm^{-1}$). Thin-layer chromatography (TLC) was carried out using precoated silica gel sheets. Visual detection was performed using ceric ammonium nitrate or *p*-anisaldehyde stains. Flash chromatography was performed using SilicaFlash P60 (60 A, 40−63 $\mu$m) silica gel with compressed air.

**3-((4a*R*,6*S*,8a*S*)-6-((1,1-Dimethylethyl)dimethylsilyloxy)-8a-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)but-3-en-2-one (3).** The allylic alcohol **11** (11.7 g, 33.3 mmol) was dissolved in DCM (330 mL), and pyridine (26.8 mL, 332.5 mmol) was added. The resulting solution was cooled to 0 °C, and Dess Martin periodinane (21.2 g, 49.9 mmol) was added gradually over 5 min. The mixture was allowed to stir for 2 h. After completion, as monitored by TLC (10:1 hexanes/ethyl acetate), the reaction was diluted with diethyl ether (400 mL) and filtered through a pad of Celite. After removal of the solvent in vacuo, the residue was purified by flash column chromatography on silica gel (20:1 hexanes/ethyl acetate with 1% TEA) to yield the dienone **3** (10.84 g, 94%) as a clear oil. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$: 5.85 (bs, 1H), 5.46 (d, $J$ = 1.3 Hz, 1H), 5.40 (dd, $J$ = 3.8, 3.8 Hz, 1H), 3.88−3.83 (m, 1H), 2.30 (s, 3H), 2.08−2.04 (m, 2H), 1.78−1.69 (m, 2H), 1.61−1.54 (m, 3H), 1.47−1.34 (m, 4H), 1.00 (s, 3H), 0.86 (s, 9H), 0.009 (s, 3H), 0.003 (s, 3H). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$: 200.8, 151.7, 142.3, 127.7, 124.6, 67.3, 38.1, 36.7, 31.4, 30.9, 26.9, 25.84, 25.77, 24.5, 24.1, 18.1, −4.9, (1 upfield carbon not observed). FTIR (DCM): 3052, 2982, 2680, 2402, 2302, 1676, 1598, 1536, 1420, 1264, 894, 730 $cm^{-1}$. HRMS (ESI TOF) $m/z$: $(M + H)^+$ Calcd for $C_{21}H_{37}O_2Si$, 349.2563; found, 349.2560. $[\alpha]_D^{21}$ −12.5° ($c$ 1.0, $CHCl_3$).

**(*S*)-((1,1-Dimethylethyl)dimethylsilyloxy)-(2-methyl-3-triethylsilyloxycyclopent-2-en-1-yl)-methoxysilane (4).** The silyl enol ether **22** (5.37 g, 17.1 mmol), used crude from the previous step, was dissolved in dimethoxyethane (170 mL) that was freshly distilled from sodium/benzophenone. To the solution was added methyllithium (MeLi, 20.5 mL of 1.0 M solution in diethyl ether, 20.5 mmol) at 21 °C, and the reaction was allowed to stir for 1 h. To the reaction was added a mixture of TESCl (3.72 mL, 22.2 mmol) and triethylamine (2.08 mL, 22.2 mmol) after removing any precipitate via centrifuge. The resulting solution was allowed to stir for an additional 30 min and quenched with saturated $NaHCO_3$ (200 mL) and diluted with hexanes (200 mL). The organic layer was collected and the aqueous layer was extracted with hexanes (2 × 100 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), and then dried over anhydrous $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by flash column chromatography on silica gel (50:1 hexanes/diethyl ether and 3% TEA) to yield the silyl enol ether **4** (4.92 g, 81%) as a clear oil. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$: 3.62 (dd, $J$ = 9.7, 4.9 Hz, 1H), 3.40 (dd, $J$ = 9.7, 7.2 Hz, 1H), 2.58−2.51 (m, 1H), 2.33−2.25 (m, 1H), 2.23−2.16 (m, 1H), 1.94−1.86 (m 1H), 1.65−1.57 (m, 1H), 1.53 (s, 3H), 0.98 (t, $J$ = 7.9 Hz, 9H), 0.89 (s, 9H), 0.64 (q, $J$ = 7.9 Hz, 6H), 0.04 (s, 6H). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$: 148.0, 113.6, 66.2, 47.7, 32.4, 26.0, 23.8, 18.3, 10.6, 6.7, 5.4, −5.3, −5.4. HRMS (ESI TOF) $m/z$: $(M + H)^+$ Calcd for $C_{19}H_{41}O_2Si_2$, 357.2645; found, 357.2649. $[\alpha]_D^{21}$ −7.7° ($c$ 1.0, $CHCl_3$).

**(4a*R*,6*S*,8a*S*)-6-Hydroxy-8a-methyloctahydronaphthalen-1(2*H*)-one (8).** The ketal 7 (4.98 g, 22.2 mmol) was dissolved in THF (50 mL) and *t*-butanol (50 mL), and the resulting solution was cooled to −78 °C using a dry ice and acetone bath. A dry ice filled condenser was added to the flask, and anhydrous ammonia (100 mL) was condensed into the reaction vessel. The external cooling bath was removed, and lithium wire was gradually added to the reaction until the blue color persisted for at least 30 min. To the reaction was added 1 M HCl (100 mL), followed by concentrated HCl, until the solution became acidic. The reaction was allowed to warm to 21 °C and stirred for 2 h. The resulting mixture was saturated with solid NaCl and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by flash column chromatography on silica gel (1:1 hexanes/ethyl acetate) to yield the alcohol **8**[8] (3.65 g, 90%) as a clear oil. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$: 4.00 (m, 1H), 2.47−2.36 (m, 1H), 2.29−2.22 (m, 1H), 2.20−1.14 (m, 1H), 2.09−2.05 (m, 1H), 2.03−1.96 (m, 1H), 2.04−1.82 (m, 2H), 1.78−1.65 (m, 2H), 1.55−1.45 (m, 4H), 1.32−1.24 (m, 1H), 1.18 (s, 3H). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$: 216.0, 66.2, 48.7, 40.0, 39.9, 37.7, 35.4, 30.0, 28.5, 26.3, 23.2. $[\alpha]_D^{21}$ −0.6° ($c$ 1.0, $CHCl_3$).


dx.doi.org/10.1021/jo400909t | J. Org. Chem. 2013, 78, 7518−7526

**(4a*R*,6*S*,8a*S*)-6-((1,1-Dimethylethyl)dimethylsilyloxy)-8a-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl Trifluoromethanesulfonate (9).** The alcohol **8** (3.65 g, 20 mmol) was dissolved in anhydrous DMF (40 mL). To the solution were added imidazole (2.99 g, 44 mmol) and *t*-butyldimethylsilyl chloride (TBSCl, 4.50 g, 30 mmol). The reaction was allowed to stir for 2 h and quenched with saturated $NaHCO_3$ (100 mL) and diluted with diethyl ether (50 mL). The organics were collected, and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by flash column chromatography on silica gel (10:1 hexanes/ethyl acetate) to yield the silyl ether (4.62 g, 78%) as a white glass. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$: 3.91 (m, 1H), 2.38 (ddd, $J$ = 14.9, 11.0, 6.8 Hz, 1H), 2.13 (ddd, $J$ = 15.1, 5.3, 5.3 Hz, 3H), 1.85−1.68 (m, 3H), 1.53−1.45 (m, 1H), 1.41−1.31 (m, 4H), 1.25 (ddd, $J$ = 13.3, 11.1, 4.0 Hz, 1H), 1.11 (s, 3H), 0.78 (s, 9H), 0.0 (s, 6H). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$: 215.9, 66.9, 48.9, 39.6, 37.8, 36.3, 20.5, 28.5, 26.3, 25.7, 25.6, 23.1, 18.0, −4.95, −4.98. HRMS (ESI TOF) $m/z$: (M + H)$^+$ Calcd for $C_{17}H_{33}O_2Si$, 297.2250; found, 297.2260. $[\alpha]_D^{21}$ −6.4° ($c$ 1.0, $CHCl_3$).

To a solution of dry diisopropylamine (5.45 mL, 39.0 mmol) in anhydrous THF (40 mL) stirred at −78 °C under argon was added *n*-butyllithium (22.5 mL of a 1.6 M solution in hexanes, 36.0 mmol) dropwise, and the resulting solution was allowed to stir for 30 min. The silyl ether was added (8.90 g, 30.1 mmol) as a solution in THF (30 mL) over 30 min, and the solution was allowed to stir for an additional 30 min. The reaction was warmed to 0 °C and stirred for 1 h. A solution of *N*-phenyl triflimide ($PhNTf_2$, 11.80 g, 33.0 mmol) in THF (30 mL) was added over 15 min, and the reaction was stirred for 1 h at the same temperature. The reaction was quenched with saturated $NaHCO_3$ (100 mL) and diluted with diethyl ether (100 mL). The organics were collected, and the aqueous layer was extracted with diethyl ether (2 × 100 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by flash column chromatography on silica gel (20:1 hexanes/diethyl ether) to yield the vinyl triflate **9** (12.40 g, 96%) as a white oil. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$: 5.65 (dd, $J$ = 8.0, 8.0 Hz, 1H), 3.92 (m, 1H), 2.22−2.16 (m, 2H), 1.97−1.91 (m, 1H), 1.82−1.76 (m, 1H), 1.70−166 (m, 2H), 1.59−1.44 (m, 5H), 1.22 (s, 3H), 0.89 (s, 9H), 0.04 (s, 6H). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$: 154.9, 118.3 (q, $J$ = 312.5 Hz), 115.9, 66.7, 38.3, 37.9, 35.6, 30.4, 28.9, 25.7, 23.5, 22.5, 18.0, −4.86, −4.90, (1 upfield carbon not observed). $[\alpha]_D^{21}$ +0.1° ($c$ 1.0, $CHCl_3$).

**3-((4a*R*,6*S*,8a*S*)-6-((1,1-Dimethylethyl)dimethylsilyloxy)-8a-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)but-3-en-2-ol (11).** The compound was prepared by a modification of the known procedure.[9a] A Schlenk flask was charged with LiCl (4.75 g, 112.20 mmol) and flame-dried under high vacuum. After the flask was cool, $Pd(PPh_3)_4$ (2.16 g, 1.87 mmol) and CuCl (9.26 g, 93.50 mmol) were added, and the mixture was degassed (4×) under high vacuum with an Ar purge. A solution of the vinyl triflate **9** (8.0 g, 18.7 mmol) and vinyl stannane **10** (8.1 g, 22.4 mmol) in DMSO (150 mL) was added via cannula, and the resulting mixture was rigorously degassed (4×) by the freeze−thaw process (−78 to 25 °C, Ar). The reaction mixture was stirred at 21 °C for 1 h, and then heated to 60 °C for 48 h. After completion, as monitored by TLC (10:1 hexanes/ethyl acetate), the reaction was cooled to 21 °C, diluted with diethyl ether (1.0 L), and washed with a mixture of brine (200 mL) and 5% aqueous $NH_4OH$ (40 mL). The aqueous layer was extracted with diethyl ether (2 × 300 mL), and the combined organic layers were washed with water (2 × 200 mL) and brine (2 × 200 mL) and then dried over anhydrous $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by flash column chromatography on silica gel (10:1 hexanes/ethyl acetate) to yield the allylic alcohol **11** (5.82 g, 87%) as a 4:5 mixture of inseparable diastereomers (determined by $^1$H NMR analysis). $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$: 5.48−5.46 (dd, $J$ = 3.9, 3.6 Hz, 0.44H), 5.46−5.45 (dd, $J$ = 3.8, 3.7 Hz, 0.56H), 5.17−5.16 (m, 0.56H), 5.14−5.13 (m, 0.44 H), 4.85−4.83 (m, 0.44H), 4.82−4.80 (m, 0.56H), 4.46 (q, $J$ = 6.5 Hz, 0.56H), 4.39 (q, $J$ = 6.8 Hz, 0.44H), 3.96−3.90 (m, 1H), 2.07−1.99 (m, 2H), 1.89−1.74 (m, 2H), 1.66−1.60 (m, 1H), 1.57−1.36 (m, 6H), 1.31 (d, $J$ = 6.7 Hz, 1.30H), 1.26 (d, $J$ = 6.4 Hz, 1.70H), 1.18 (s, 1.3 H), 1.15 (s, 1.7H), 0.88 (s, 9H), 0.04−0.00 (m, 6H). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$: 155.1, 129.4, 127.1, 127.0, 126.6, 123.5, 111.8, 110.5, 69.1, 68.6, 67.1, 36.5, 36.4, 31.2, 31.0, 30.96, 25.8, 25.8, 24.0, 23.8, 22.6, 21.3, 18.08, 18.06, −4.9. HRMS (ESI-TOF) $m/z$: (M + Na)$^+$ Calcd for $C_{21}H_{38}O_2SiNa$, 373.2539; found, 373.2538.

**Triethyl((2-methyl-3-ethenylcyclopent-1-en-1-yl)oxy)silane (12).** The compound was prepared by a modification of the known procedure.[13] A suspension of CuI (9.5 g, 49.9 mmol) in 100 mL of THF was cooled to −20 °C under an atmosphere of argon, and vinylmagnesium bromide was added (100 mL of 1.0 M solution in THF, 100 mmol). The resulting black mixture was allowed to stir for 0.5 h and subsequently cooled to −40 °C. To this solution was added 2-methyl-2-cyclopenten-1-one (4.0 g, 41.6 mmol) via cannula as a solution in 10 mL of THF, and the reaction was allowed to stir for 1 h. The reaction was cooled to −78 °C and HMPA (75 mL, 416 mmol), followed by TESCl (21 mL, 125 mmol), were added, and the reaction was allowed to warm to 21 °C overnight. The reaction was quenched with a minimal amount of saturated $NaHCO_3$ until no further bubbling was apparent. The crude reaction mixture was filtered over Celite, and the filter cake was washed with hexanes. The filtrates were washed with saturated $NaHCO_3$ (100 mL). The organics were collected, and the aqueous layer was extracted with hexanes (2 × 50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), and then dried over anhydrous $MgSO_4$. After removal of the solvent in vacuo, the residue was distilled under reduced pressure (49 °C, 0.5 mmHg) to yield the pure silyl enol ether (6.44 g, 65%). $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$: 5.62 (ddd, $J$ = 21.3, 12.2, 10.6 Hz, 1H), 4.98 (dd, $J$ = 21.3, 2.5 Hz, 1H), 4.91 (dd, $J$ = 12.5, 2.5 Hz, 1H), 3.03−2.94 (m, 1H), 2.36−2.24 (m, 2H), 2.11−2.01 (m, 1H), 1.61−1.53 (m, 1H), 1.47 (s, 3H), 0.99 (t, $J$ = 10 Hz, 9H), 0.65 (q, $J$ = 10 Hz, 6H). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$: 147.8, 142.9, 114.6, 113.3, 40.1, 32.7, 27.5, 10.3, 6.6, 5.4. FTIR (DCM): 2991, 1685, 1630, 1245, 1211, 1093, 989, 839 cm$^{-1}$.

**1-((3*S*,5*R*,10*S*)-3-((1,1-Dimethylethyl)dimethylsilyloxy)-10,13-dimethyl-14-(triethylsilyloxy)-17-ethenyl-2,3,4,5,6,7,8,10,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-11-yl)ethanone (13).** The catalyst MeAl-$(NTf_2)_2$ was prepared by addition of $Tf_2NH$ (0.5 mL of 0.1 M solution in DCM, 0.05 mmol) to trimethylaluminum ($Me_3Al$, 0.3 mL of 0.1 M solution in toluene, 0.03 mmol) in 4 mL of DCM at 21 °C, and the solution was allowed to stir for 15 min. The reaction was cooled to 0 °C, and the dienone **3** (0.5 mmol) and the silyl enol ether **12** (0.65 mmol) were added in 1 mL of DCM. The reaction was warmed to 21 °C and allowed to stir for 2 h. The reaction was quenched with addition of TEA (0.5 mL) and filtered through a plug of silica gel. After removal of the solvent in vacuo, the residue was purified by flash column chromatography on silica gel (2:1 hexanes/benzene to benzene) to yield the tetracycles as a separable 1:1 mixture of diastereomers. Structures assigned by comparison of spectra to compounds **23** and **24**. **13A**: 128.5 mg, 45%. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$: 5.72 (ddd, $J$ = 16.4, 9.2, 9.2 Hz, 1H), 4.99 (d, $J$ = 10 Hz, 1H), 4.92 (d, $J$ = 17.3 Hz, 1H), 3.96 (m, 1H), 2.31 (s, 3H), 2.30−2.24 (m, 1H), 2.17−2.11 (m, 1H), 2.01 (dd, $J$ = 16.5, 3.7 Hz, 1H), 1.93−1.76 (m, 4H), 1.71−1.53 (m, 8H), 1.41 (bd, $J$ = 12.9 Hz, 1H), 1.38−1.32 (m, 1H), 1.30−1.22 (m, 2H), 1.18 (s, 3H), 0.94 (t, $J$ = 8 Hz, 9H), 0.86 (s, 9H), 0.78 (s, 3H), 0.62 (q, $J$ = 8 Hz, 6H), 0.00 (s, 6H). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$: 208.5, 140.4, 132.0, 128.4, 115.7, 83.9, 67.4, 46.2, 41.1, 38.1, 36.5, 34.3, 32.2, 31.6, 30.9, 30.2, 28.9, 27.1, 25.9, 25.8, 22.7, 21.9, 18.5, 18.1, 14.2, 7.4, 6.9, −4.80, −4.81. FTIR (DCM): 3052, 2984, 2952, 2926, 2874, 2306, 1686, 1420, 1264, 1138, 1080, 1056 cm$^{-1}$. HRMS (ESI TOF) $m/z$: (M + H)$^+$ Calcd for $C_{35}H_{62}O_3Si_2$, 587.4316; found, 587.4337. $[\alpha]_D^{21}$ +4.9° ($c$ 1.0, $CHCl_3$). **13B**: 134.2 mg, 47%. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$: 5.66 (ddd, $J$ = 16.8, 9.2, 8.3 Hz, 1H), 4.97 (d, $J$ = 10 Hz, 1H), 4.91 (d, $J$ = 17 Hz, 1H), 3.82−3.75 (m, 1H), 2.29 (s, 3H), 2.29−2.24 (m, 1H), 2.0 (m, 2H), 1.85−1.75 (m, 4H), 1.73−1.55 (m, 7H), 1.52−1.43 (m, 3H), 1.31−1.18 (m, 5H), 0.95 (t, $J$ = 7.9 Hz, 9H), 0.88 (s, 9H), 0.75 (s, 3H), 0.62 (q, $J$ = 7.9 Hz, 6H), 0.04 (s, 6H). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$: 210.5, 139.9,


dx.doi.org/10.1021/jo400909t | J. Org. Chem. 2013, 78, 7518−7526

137.2, 132.2, 116.0, 83.8, 67.5, 46.0, 45.7, 43.0, 42.7, 40.0, 38.4, 34.9, 34.4, 32.6, 32.0, 30.5, 29.9, 27.4, 26.0, 25.9, 25.6, 18.4, 18.3, 7.4, 7.0, −4.59, −4.63. FTIR (DCM): 3054, 2978, 2950, 2922, 2880, 2301, 1690, 1411, 1265, 1138, 1072, 1056 $cm^{-1}$. HRMS (ESI TOF) *m/z*: $(M + H)^+$ Calcd for $C_{35}H_{62}O_3Si_2$, 587.4316; found, 587.4307. $[\alpha]_D^{21}$ +12.5° (*c* 1.0, $CHCl_3$).

**((3-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-methylcyclopent-1-en-1-yl)oxy)triethylsilane (16).** The silyl enol ether **19** (0.070 g, 0.23 mmol) was dissolved in chloroform (5 mL), and Wilkinson's catalyst ($RhCl(Ph_3P)_3$, 11 mg, 0.012 mmol) was added. The solution was heated to 61 °C and allowed to stir for 14 h. The reaction was allowed to cool and filtered through a pad of silica gel previously deactivated with TEA. After removal of the solvent in vacuo, the residue was purified by flash column chromatography on silica gel (40:1 hexanes/ethyl acetate and 1% TEA) to yield the silyl enol ether **16** (0.050 g, 72%) as a ∼1:1 mixture (determined by $^1$H NMR analysis) of inseparable diastereomers (structures unassigned). $^1$H NMR ($CDCl_3$, 400 MHz) *δ*: 4.21 (ddd, *J* = 7.3, 7.2, 6.3, 0.95H), 4.05−3.98 (m, 2H), 3.90 (dd, *J* = 7.6, 6.4 Hz, 0.95H), 3.59 (dd, *J* = 6.8, 6.8 Hz, 1H), 3.55 (dd, *J* = 7.5, 7.5 Hz, 0.95H), 2.83−2.76 (m, 0.95H), 2.62−2.56 (m, 1H), 2.37−2.17 (m, 3.9H), 2.00−1.83 (m, 1.95H), 1.79−1.71 (m, 0.95H), 1.63−1.57 (m, 1H), 1.57 (bs, 2.85H), 1.54 (bs, 3H), 1.43 (s, 3H), 1.40 (s, 3H), 1.34 (s, 5.7H), 0.98 (t, *J* = 7.3 Hz, 17.6H), 0.65 (q, *J* = 7.3 Hz, 6H), 0.64 (q, *J* = 7.3 Hz, 5.7H). $^{13}$C NMR ($CDCl_3$, 100 MHz) *δ*: 157.7, 154.9, 129.0, 126.5, 108.1, 95.9, 78.6, 78.4, 67.7, 66.5, 47.7, 47.0, 32.8, 32.6, 32.5, 26.4, 25.6, 25.1, 24.2, 23.1, 21.0, 11.1, 10.9, 6.6, 5.41, 5.38. HRMS (ESI-TOF) *m/z*: $(M + Li)^+$ Calcd for $C_{17}H_{32}O_3SiLi$, 319.2281; found, 319.2268.

**4-((1,1-Dimethylethyl)dimethylsilyloxy)-3-(1,2-dihydroxyethyl)-2-methylcyclopentanone (17).** The TBS ether **14**, *N*-methylmorpholine-*N*-oxide (NMO, 0.43 g, 3.7 mmol), and citric acid monohydrate (0.446 g, 2.12 mmol) were dissolved in a mixture of 1:1 *t*-BuOH/$H_2O$ (3 mL). Osmium tetroxide ($OsO_4$, 0.283 mL of 0.1 M solution in $H_2O$, 0.0283 mmol) was added, and the solution was allowed to stir for 14 h. The reaction was diluted with ethyl acetate (10 mL) and water (10 mL). The organic layer was collected, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (10 mL) and dried over anhydrous $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by flash column chromatography on silica gel (1:1 hexanes/ethyl acetate) to yield the diol **17** (0.46 g, 56%) as a 3:2 mixture (determined by $^1$H NMR analysis) of inseparable diastereomers (structures unassigned). $^1$H NMR ($CDCl_3$, 500 MHz) *δ*: 4.70 (ddd, *J* = 8.0, 7.7, 7.7 Hz, 1H), 4.31 (ddd, *J* = 8.0, 8.0, 7.2 Hz, 0.66H), 3.98−3.93 (m, 0.66H), 3.88−3.84 (m, 1H), 3.76−3.62 (m, 3.3H), 3.16 (bm, 1H), 2.98−2.90 (bm, 0.66H), 2.81−2.57 (m, 3.3H), 2.27−2.15 (m, 3.3H), 1.89−1.81 (m, 1.66H), 1.17 (d, *J* = 7.2 Hz, 2H)), 1.13 (d, *J* = 7.5 Hz, 3H), 0.88 (s, 9H), 0.12 (s, 3H), 0.9 (s, 2H), 0.07 (s, 3H), 0.6 (s, 2H). $^{13}$C NMR ($CDCl_3$, 125 MHz) *δ*: 217.1, 216.1, 71.8, 71.4, 70.1, 68.7, 65.6, 65.4, 54.8, 54.3, 47.2, 47.2, 45.5, 43.9, 25.6, 25.6, 17.7, 17.6, 15.4, 13.1, −4.0, −4.5, −4.9, −5.0. HRMS (ESI TOF) *m/z*: $(M + Na)^+$ Calcd for $C_{14}H_{28}O_4SiNa$, 311.1655; found, 311.1651.

**3-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-methylcyclopentanone (18).** The diol **17** (0.46 g, 1.6 mmol) was dissolved in a 1:1:1 mixture of THF/trifluoroacetic acid/$H_2O$ (6 mL) and allowed to stir for 2 h. The crude reaction mixture was concentrated in vacuo at 60 °C and subsequently azeotroped with benzene (3 × 5 mL). The crude product was redissolved in dimethoxypropane (5 mL), and camphorsulfonic acid (CSA, 7.4 mg, 0.032 mmol) was added. The solution was allowed to stir for 2 h, quenched with saturated $NaHCO_3$ (10 mL) and diluted with ethyl acetate (10 mL). The organic layer was collected, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine (10 mL), and then dried over anhydrous $MgSO_4$. After removal of the solvent in vacuo, the residue was dissolved in methanol (5 mL), and palladium on carbon (10 wt %, 46 mg) was added. The reaction was equipped with a balloon of hydrogen gas, and stirred vigorously for 3 h. The reaction vessel was subsequently purged with argon gas and filtered over Celite, and the filter cake was further washed with ethyl acetate. After removal of the solvent in vacuo, the residue was purified by flash column chromatography on silica gel (10:1 hexanes/ethyl acetate) to yield the acetonide **18** (0.146 g, 46%) as a 5:4 mixture (determined by $^1$H NMR analysis) of inseparable diastereomers (structures unassigned). $^1$H NMR ($CDCl_3$, 400 MHz) *δ*: 4.19−4.13 (m, 1H), 4.10−4.02 (m, 2H), 3.71−3.64 (m, 1.6H), 3.22−3.14 (m, 0.8H), 2.44−2.30 (m, 2H), 2.19−2.06 (m, 3H), 2.03−1.71 (m, 5H), 1.57−1.47 (m, 0.8H), 1.41 (s, 3H), 1.39 (s, 2.4H), 1.26 (s, 3H), 1.34 (s, 2.4H), 1.18 (d, *J* = 7.0 Hz, 2.4H), 1.08 (d, *J* = 7.0 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) *δ*: 220.4, 220.0, 109.2, 108.8, 79.8, 76.8, 67.7, 67.4, 48.0, 47.5, 46.9, 46.5, 36.84, 36.79, 26.6, 26.4, 25.5, 25.4, 23.4, 22.1, 14.5, 13.0. HRMS (ESI TOF) *m/z*: $(M + Na)^+$ Calcd for $C_{11}H_{18}O_3Na$, 221.1154; found, 221.1148.

**((4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-5-methylcyclopent-1-en-1-yl)oxy)triethylsilane (19).** A solution of the acetonide **18** (0.05 g, 0.25 mmol) in DCM (5 mL) was cooled to −78 °C under argon. To the solution was added DIPEA (0.065 mL, 0.375 mmol), followed by TESOTf (0.099 mL, 0.375 mmol). The solution was allowed to stir for 0.5 h at −78 °C, then warmed to 21 °C and stirred for an additional 2 h. The reaction was quenched with saturated $NaHCO_3$ (10 mL) and diluted with hexanes (10 mL), the organic layer was collected, and the aqueous layer was extracted with hexanes (2 × 10 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by flash column chromatography on silica gel (40:1 hexanes/ethyl acetate and 3% TEA) to yield the silyl enol ether **19** (0.070 g, 90%) as a 10:9 mixture (determined by $^1$H NMR analysis) of inseparable diastereomers (structures unassigned). $^1$H NMR ($CDCl_3$, 500 MHz) *δ*: 4.50−4.47 (m, 1H), 4.47−4.45 (m, 0.9H) 4.12−4.06 (m, 1.8H), 4.04−3.96 (m, 2H), 3.62−3.56 (m, 1.9H), 2.45−2.36 (m, 1.8H), 2.32−2.24 (m, 2H), 2.14−2.09 (m, 1H), 2.00−1.92 (m, 1.9H), 1.88−1.82 (m, 0.9H), 1.42 (bs, 5.4H), 1.35 (bs, 6H), 1.12 (d, *J* = 7.1 Hz, 2.7H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.97 (t, *J* = 7.9 Hz, 17.1H), 0.67 (q, *J* = 7.9 Hz, 11.4H). $^{13}$C NMR ($CDCl_3$, 125 MHz) *δ*: 157.3, 156.7, 108.6, 108.4, 98.6, 98.4, 79.7, 78.8, 67.6, 67.6, 46.7, 46.5, 43.1, 41.7, 29.7, 29.1, 26.8, 26.6, 25.42, 25.40, 18.8, 18.3, 6.7, 6.5, 4.62, 4.61. HRMS (ESI-TOF) *m/z*: $(M + Li)^+$ Calcd for $C_{17}H_{32}O_3SiLi$, 319.2281; found, 319.2297.

**1-((3*S*,5*R*,8*R*,10*S*,13*R*,14*S*,17*S*)-3-((1,1-Dimethylethyl)dimethylsilyloxy)-17-(((1,1-dimethylethyl)dimethylsilyloxy)methyl)-10,13-dimethyl-14-((triethylsilyl)oxy)-2,3,4,5,6,7,8,10,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-11-yl)ethanone (23 and 24).** The catalyst $Me_2AlNTf_2$ was prepared by addition of $Tf_2NH$ (0.25 mL of 0.1 M solution in DCM, 0.025 mmol) to trimethylaluminum ($Me_3Al$, 0.3 mL of 0.1 M solution in toluene, 0.03 mmol) in 4 mL of DCM at 21 °C, and the solution was allowed to stir for 15 min. The reaction was cooled to −20 °C, and the dienone **3** (0.174 g, 0.5 mmol) and the silyl enol ether **4** (0.178 g, 0.65 mmol) were added in 1 mL of DCM and allowed to stir for 4 h. The reaction was quenched with addition of TEA (0.5 mL) and filtered through a plug of silica gel. After removal of the solvent in vacuo, the residue was purified by flash column chromatography on silica gel (20:1 hexanes/ethyl acetate) to yield the tetracycles **23** (254 mg, 72%) as a 10:1 mixture (determined by $^1$H NMR analysis) of separable diastereomers. **23:** 229 mg, 65%. $^1$H NMR ($CDCl_3$, 500 MHz) *δ*: 3.81−3.76 (m, 1H), 3.58 (dd, *J* = 9.9, 7.9 Hz, 1H), 3.49 (dd, *J* = 9.9, 7.0 Hz, 1H), 2.28 (s, 3H), 2.05−1.99 (m, 2H), 1.96−1.90 (m, 2H), 1.83−1.65 (m, 6H), 1.64−1.44 (m, 5H), 1.33−1.24 (m, 4H), 1.12 (s, 3H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.83 (s, 3H), 0.61 (q, *J* = 8.0 Hz, 6H), 0.07 (s, 6H), 0.04 (s, 6H). $^{13}$C NMR ($CDCl_3$, 125 MHz) *δ*: 210.2, 137.0, 132.5, 84.3, 67.5, 65.2, 44.2, 42.71, 42.66, 42.2, 40.0, 38.4, 36.1, 34.0, 32.6, 32.1, 30.5, 30.3, 29.9, 29.7, 27.4, 25.99, 25.97, 23.3, 18.3, 18.0, 7.4, 7.0, −4.59, −4.61, −5.3, −5.4. HRMS (ESI TOF) *m/z*: $(M + Na)^+$ Calcd for $C_{40}H_{76}O_4Si_3Na$, 727.4949; found, 727.4953. $[\alpha]_D^{21}$ +9.6° (*c* 1.0, $CHCl_3$). **24**: 25 mg, 7%. $^1$H NMR ($CDCl_3$, 500 MHz) *δ*: 3.97−3.92 (m, 1H), 3.62 (dd, *J* = 9.9, 8.5 Hz, 1H), 3.53 (dd, *J* = 10.3, 6.6 Hz, 1H), 2.33 (s, 3H), 2.31−2.27 (m, 1H), 2.20−2.13 (m, 1H), 2.09−2.03 (m, 1H), 2.02−1.84 (m, 4H), 1.83−1.51 (m, 8H), 1.46−1.39 (m, 2H), 1.37−1.31 (m, 2H), 1.25 (s, 3H), 1.19 (s, 3H), 0.94 (t, *J* = 7.7 Hz,


dx.doi.org/10.1021/jo400909t | J. Org. Chem. 2013, 78, 7518−7526

9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.61 (q, $J$ = 7.7 Hz, 6H), 0.03 (s, 6H), 0.00 (s, 6H). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$: 208.6, 132.3, 127.8, 84.4, 67.4, 65.6, 44.5, 41.1, 40.8, 38.1, 36.5, 33.8, 32.2, 30.9, 30.3, 29.7, 27.1, 26.0, 25.95, 25.88, 25.7, 23.1, 21.9, 18.5, 18.1, 18.0, 7.4, 7.0, −4.80, −4.82, −5.3, −5.4. HRMS (ESI TOF) $m/z$: (M + Na)$^+$ Calcd for $C_{40}H_{76}O_4Si_3Na$, 727.4949; found, 727.4940.

**1-((3*S*,5*R*,8*R*,10*S*,13*S*,14*R*,17*R*)-3,14-Dihydroxy-17-(hydroxymethyl)-10,13-dimethyl-2,3,4,5,6,7,8,10,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-11-yl)-ethanone (25).** The tetracycle **24** (0.350 mg, 0.49 mmol) was dissolved in methanol (2 mL), and camphorsulfonic acid (11.0 mg, 0.049 mmol) was added. The resulting solution was allowed to stir for 24 h and quenched with saturated $NaHCO_3$ (5 mL) and diluted with ethyl acetate (5 mL). The organic layer was collected, and the aqueous layer was extracted with ethyl acetate (2 × 5 mL). The combined organic layers were washed with brine (5 mL), and then dried over anhydrous $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by flash column chromatography on silica gel (ethyl acetate to ethyl acetate/1% MeOH) to yield the triol **25** (0.109 g, 61%) as a clear oil. An analytical crystal sample was obtained by slow evaporation of ethyl acetate. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$: 3.87−3.80 (m, 1H), 3.70 (dd, $J$ = 10.5, 3.6 Hz, 1H), 3.58 (dd, $J$ = 10.6, 4.8 Hz, 1H), 2.50−2.43 (m, 1H), 2.32 (s, 3H), 2.12−2.08 (m, 1H), 2.07−2.03 (m, 2H), 2.02−1.96 (m, 2H), 1.92−1.87 (m, 1H), 1.83−1.80 (m, 3H), 1.73−1.66 (m, 5H), 1.61−1.57 (m, 2H), 1.54−1.50 (m, 1H), 1.46−1.39 (m, 1H), 1.37−1.32 (m, 1H), 1.20 (s, 3H), 1.11−1.07 (m, 1H), 1.02 (s, 3H), 0.98−0.91 (m, 1H). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$: 209.7, 132.4, 124.9, 80.7, 66.8, 62.9, 44.1, 40.1, 39.0, 38.8, 36.5, 31.3, 31.1, 30.6, 30.1, 26.5, 21.7, 21.0, 20.6, 19.1, 18.2, 16.9. HRMS (ESI TOF) $m/z$: (M + Na)$^+$ Calcd for $C_{22}H_{34}O_4Na$, 385.2355; found, 385.2362.

**1-((3*S*,5*R*,8*S*,10*S*,13*R*,14*S*,17*S*)-((1,1-Dimethylethyl)dimethylsilyloxy)-17-(((1,1-dimethyl-ethyl)dimethylsilyloxy)methyl)-10,13-dimethyl-14-((triethylsilyl)oxy)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-11-yl)ethanone (26).** Anhydrous ammonia ($NH_3$, 10 mL) was condensed via a coldfinger filled with a mixture of dry ice and acetone onto strips of lithium (Li, 0.032 g, 4.6 mmol) and allowed to reflux for 1 h and subsequently cooled to −78 °C. A solution of the tetracycle **23** (0.653 g, 0.926 mmol) in THF (10 mL) was added via cannula. The reaction was allowed to stir for 30 min, and any unreacted lithium was quenched with freshly distilled isoprene until the blue color dispersed completely. The ammonia was removed under a flow of argon and with gradual warming to room temperature. The resulting solution was quenched with saturated $NaHCO_3$ (10 mL) and diluted with diethyl ether (20 mL). The organic layer was collected, and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous $MgSO_4$. After removal of the solvent in vacuo, the residue was redissolved in a small amount of ether and purified over a short plug of silica gel (5 g), yielding 0.630 mg of crude product as a mixture of diastereomers. After removal of the solvent in vacuo, the residue was dissolved in DCM (10 mL), and pyridine (0.075 mL, 0.926 mmol) and Dess−Martin periodinane were added (0.20 g, 0.46 mmol). The mixture was allowed to stir for 4 h, diluted with diethyl ether (10 mL), and filtered through a pad of Celite. After removal of the solvent in vacuo, the residue was purified by flash column chromatography on silica gel (20:1 hexanes/diethyl ether) to yield the compound **26** (0.406 g, 62%) as a clear oil. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$: 3.84−2.75 (m, 1H), 3.61 (dd, $J$ = 9.5, 6.4 Hz, 1H), 3.47 (dd, $J$ = 9.3, 7.3 Hz, 1H), 2.91−2.83 (m, 1H), 2.50−2.42 (m, 1H), 2.22 (s, 3H), 2.17−2.13 (m, 1H), 2.03−1.96 (m, 2H), 1.92−1.88 (m, 2H), 1.75−1.71 (m, 1H), 1.69−1.66 (m, 3H), 1.62−1.60 (m, 1H), 1.50−1.44 (m, 4H), 1.44−1.42 (m, 1H), 1.39−1.30 (m, 2H), 1.29−1.22 (m, 2H), 0.91 (t, $J$ = 7.4 Hz, 9H), 0.98 (s, 3H), 0.97 (s, 3H), 0.872 (s, 9H), 0.867 (s, 9H), 0.64 (q, $J$ = 7.4 Hz, 6H), 0.04 (s, 6H), 0.01 (s, 6H). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$: 213.0, 87.1, 67.3, 65.7, 46.7, 44.6, 44.5, 42.2, 41.9, 38.3, 37.7, 37.1, 36.9, 36.6, 31.9, 31.3, 29.3, 28.48, 28.45, 25.99, 25.95, 25.9, 25.8, 25.3, 24.2, 18.3, 7.5, 6.8, −4.5, −5.3. HRMS (ESI TOF) $m/z$: (M + Na)$^+$ Calcd for $C_{40}H_{78}O_4Si_3Na$, 729.5106; found, 729.5099.

**(((3*S*,5*R*,8*S*,10*S*,13*R*,14*S*,17*S*,*E*)-3-((1,1-Dimethylethyl)dimethylsilyloxy)-10,13-dimethyl-14-((triethylsilyl)oxy)-11-(1-((trimethylsilyl)oxy)ethylidene)hexadecahydro-1*H*-cyclopenta-[*a*]phenanthren-17-yl)methoxy)-(1,1-dimethylethyl)dimethylsilane (27).** To a solution of ketone **26** (0.703 g, 1.0 mmol) in DCM (10 mL) was added hexamethyldisilizane (HMDS, 0.417 mL, 2.0 mmol) at room temperature. To the resulting solution was added iodotrimethylsilane (TMSI, 0.210 mL, 1.5 mmol), and the resulting solution was allowed to stir for 3 h. The resulting solution was quenched with saturated $NaHCO_3$ (10 mL) and diluted with diethyl ether (20 mL). The organic layer was collected, and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous $MgSO_4$. After removal of the solvent in vacuo, the crude product was used in the next reaction without further purification.

**(3*S*,5*R*,8*S*,10*S*,13*S*,14*S*,17*S*)-3-((1,1-Dimethylethyl)dimethylsilyloxy)-17-(((1,1-dimethylethyl)dimethylsilyloxy)methyl)-12-hydroxy-10,13-dimethyl-14-((triethylsilyl)oxy)tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-11(2*H*)-one (30).** The crude silyl enol **27** (0.78 g, 1.0 mmol) was dissolved in DCM (20 mL) and cooled to −78 °C. The solution was purged with ozone until a pale blue color appeared, and triphenylphosphine (0.524 g, 2.0 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 2 h. After removal of the solvent in vacuo, the residue was purified by flash column chromatography on silica gel (20:1 hexanes/diethyl ether) to yield the compound **30** (0.117 g, 15%) as a white oil. An analytical crystal sample was obtained by slow evaporation of methanol. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$: 4.23−4.16 (m, 1H), 4.01−3.97 (m, 1H), 3.85−3.74 (m, 1H), 3.56 (dd, $J$ = 9.9, 7.4 Hz, 1H), 3.36 (dd, $J$ = 9.9, 5.6 Hz, 1H), 2.39 (d, $J$ = 13.6 Hz, 1H), 2.27 (d, $J$ = 12.4 Hz, 1H), 1.85−1.79 (m, 3H), 1.77−1.74 (m, 1H), 1.69−1.60 (m, 7H), 1.55−1.49 (m, 3H), 1.47−1.40 (m, 2H), 1.19 (s, 3H), 1.06 (s, 3H), 0.97 (t, $J$ = 7.9 Hz, 9H), 0.91 (s, 9H), 088 (s, 9H), 0.69 (q, $J$ = 7.9 Hz, 6H), 0.06 (s, 6H), 0.04 (s, 6H). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$: 211.0, 86.3, 78.8, 67.6, 64.2, 57.9, 56.6, 44.0, 43.8, 42.1, 37.2, 35.1, 31.8, 31.4, 28.8, 28.1, 26.00, 25.97, 24.2, 23.9, 22.5, 18.37, 18.36, 15.1, 7.4, 7.1, −4.5, −4.6, −5.4, −5.6. HRMS (ESI TOF) $m/z$: (M + Na)$^+$ Calcd for $C_{38}H_{74}O_5Si_3Na$, 717.4742; found, 717.4745. Acyloin **28**: 202.5 mg, 28%, 4:1 mixture (determined by $^1$H NMR analysis) of inseparable diastereomers. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$: 4.08 (s, 1.24H), 3.82−3.76 (m, 1.24H), 3.71 (dd, $J$ = 9.1, 5.6 Hz, 1.24H), 3.66 H (dd, $J$ = 9.4, 9.4 Hz, 0.24 H), 3.51 (dd, $J$ = 9.1, 9.1, 1H), 2.60 (s, 0.72H), 2.67 (s, 3H), 2.23−2.14 (m, 2.5H), 2.14−2.12 (m, 1.24H), 2.09−2.06 (m, 1.24H), 2.09−2.06 (m, 1.24H), 2.02−1.97 (m, 2.5H), 1.87−1.80 (m, 2.5H), 1.73−1.64 (m, 5.0H), 1.61−1.57 (m, 3.7H), 1.54−1.52 (m, 1.24H), 1.43−1.36 (m, 3.7H), 1.25 (s, 0.72H), 1.21 (s, 3H), 1.05 (s, 0.72H), 1.02 (t, $J$ = 7.9 Hz, 9H), 0.97 (t, $J$ = 8.5 Hz, 2.2H), 0.91 (s, 3H), 0.875 (s, 11.2H), 0.870 (s, 11.2H), 0.68 (q, $J$ = 7.9 Hz, 6H), 0.66−0.63 (m, 1.4H), 0.07 (s, 6H), 0.05 (s, 8.9 H). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$: 214.3, 132.2, 132.1, 132.0, 128.6, 128.5, 87.5, 83.9, 67.1, 66.3, 54.6, 49.4, 48.2, 46.9, 41.3, 38.6, 37.4, 37.2, 33.0, 31.9, 29.9, 29.7, 26.0, 25.9, 25.7, 24.8, 24.1, 18.3, 18.2, 17.5, 7.5, 6.8, −4.5, −4.6, −5.2, −5.3 (minor isomer not reported). HRMS (ESI TOF) $m/z$: (M + Na)$^+$ Calcd for $C_{40}H_{78}O_5Si_3Na$, 745.5055; found, 745.5057. Ketone **29**: 67.9 mg, 10%. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$: 3.79−3.71 (m, 1H), 3.67 (dd, $J$ = 9.4, 5.7 Hz, 1H), 3.48 (dd, $J$ = 9.4, 9.4 Hz, 1H), 2.59 (d, $J$ = 5.0 Hz, 1H), 2.57−2.52 (m, 1H), 2.40−2.36 (m, 1H), 2.34 (d, $J$ = 11.8 Hz, 1H), 2.16−2.09 (m, 2H), 2.06−1.98 (m, 2H), 1.90 (d, $J$ = 11.8 Hz, 1H), 1.82−1.78 (m, 1H), 1.76−1.72 (m, 4H), 1.71−1.69 (m, 1H), 1.67−1.65 (m, 1H), 1.50−1.44 (m, 2H), 1.43−1.42 (m, 1H), 1.32−1.27 (m, 2H), 1.26−1.24 (m, 3H), 1.23−1.20 (m, 2H), 1.17 (s, 3H), 1.00 (t, $J$ = 7.7 Hz, 9H), 0.99 (s, 3H), 0.87 (s, 18H), 0.68 (q, $J$ = 7.7 Hz, 3H), 0.67 (q, $J$ = 7.7 Hz, 3H), 0.04 (s, 6H), 0.02 (s, 3H), 0.01 (s, 3H). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$: 210.9, 86.7, 67.2, 65.9, 58.2, 55.3, 54.2, 54.0, 45.5, 37.8, 37.1, 36.6, 34.3, 31.3, 30.8, 30.3, 29.7, 29.3, 29.0, 25.9, 25.4, 24.6, 23.2, 23.0, 21.0, 18.3, 18.2, 17.4, 7.4, 6.7, −4.48, −4.53, −5.2, −5.3. HRMS (ESI TOF) $m/z$: (M + Na)$^+$ Calcd for $C_{38}H_{74}O_4Si_3Na$, 701.4792; found, 701.4799.


dx.doi.org/10.1021/jo400909t | J. Org. Chem. 2013, 78, 7518−7526

## ■ ASSOCIATED CONTENT

### Supporting Information

Proton and carbon NMR data for all compounds and X-ray crystallographic data (ORTEP and CIF files) for compounds **25** and **30**. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: jung@chem.ucla.edu.


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

The authors thank Dr. Saeed Khan for obtaining and analyzing the X-ray crystallographic data. This material is based upon work supported by the National Science Foundation under equipment grant no. CHE-1048804.

## ■ REFERENCES


(1) For a recent review of applications, see: Prassas, I.; Diamandis, E. P. *Nat. Rev. Drug Discovery* **2008**, *7*, 926.

(2) For isolation of rhodexin A, see: (a) Nawa, H. *Proc. Jpn. Acad.* **1951**, *27*, 436. For biological activity, see: (b) Kikuchi, K.; Chen, K. K. *J. Pharmacol. Exp. Ther.* **1964**, *146*, 365. (c) Umebayashi, C.; Yamamoto, N.; Nakao, H.; Toi, Y.; Chika-Hisa-Muramatsu, L.; Kanemaru, K.; Masuda, T.; Oyama, Y. *Biol. Pharm. Bull.* **2003**, *26*, 627. (d) 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.

(3) (a) Lin, J.; Carducci, M. A. *Expert Opin. Invest. Drugs* **2009**, *18*, 241. (b) Lin, J.; Denmeade, S.; Carducci, M. A. *Curr. Cancer Drug Targets* **2009**, *9*, 881. (c) Newman, R. A.; Yang, P.; Pawlus, A. D.; Block, K. I. *Mol. Interventions* **2008**, *8*, 36. (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.

(4) For the total synthesis of rhodexin A and further synthetic work, see: (a) Jung, M. E.; Yoo, D. *Org. Lett.* **2011**, *13*, 2698. (b) Jung, M. E.; Chu, H. V. *Org. Lett.* **2008**, *10*, 3647. (c) Jung, M. E.; Chu, H. V. *Tetrahedron Lett.* **2011**, *52*, 4512.

(5) For examples of syntheses of structurally related molecules and synthetic approaches, see: (a) Renata, H.; Zhou, Q.; Baran, P. S. *Science* **2013**, *339*, 59. (b) Hanson, J. R. *Nat. Prod. Rep.* **2005**, *22*, 104. (c) Fortner, K. C.; Kato, D.; Tanaka, Y.; Shair, M. D. *J. Am. Chem. Soc.* **2010**, *132*, 275. (d) Jana, C. K.; Hoecker, J.; Woods, T. M.; Jessen, H. J.; Neuburger, M.; Gademann, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 8407.

(6) (a) Buchschacher, P.; Fürst, A.; Gutzwiller, J. *Org. Synth.* **1990**, *7*, 368. (b) Bosch, M. P.; Camps, F.; Coll, J.; Guerrero, A.; Tatsuoka, T.; Meinwald, J. *J. Org. Chem.* **1986**, *51*, 773.

(7) Park, K.; Scott, W. J.; Wiemer, D. F. *J. Org. Chem.* **1994**, *59*, 6313.

(8) This compound has been prepared before in fairly poor yield via microbial transformation of **5**. Acklin, W.; Prelog, V.; Serdarevic, B. *Helv. Chim. Acta* **1963**, *46*, 2440.

(9) (a) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600. (b) For a review of the Stille coupling, see: Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1.

(10) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. For more convenient preparative methods, see: (b) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537. (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(11) Jung, M. E.; Ho, D. *Org. Lett.* **2007**, *9*, 375.

(12) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, *2*, 1011.

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

(14) Jung, M. E.; Ho, D.; Chu, H. V. *Org. Lett.* **2005**, *7*, 1649.

(15) For use of these mixed aluminum triflimide catalysts in other Diels–Alder cycloadditions, see: (a) Jung, M. E.; Guzaev, M. *Org. Lett.* **2012**, *14*, 5169. For other applications of these complexes, see: (b) Marx, A.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 178. (c) Boxer, M. B.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 3127. (d) Albert, B. J.; Yamaoka, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 2610.

(16) We have shown that, if one carries out and quenches this reaction at low temperature, one obtains a mixture of silyl enol ether ketones resulting from the initial Mukaiyama Michael reaction without the hindered Mukaiyama aldol having taken place. We have observed this process before in the stepwise Diels–Alder reaction of 2-silyloxydiene and enones.[11]

(17) For some relevant strategies, see: (a) Duursma, A.; Boiteau, J.-G.; Lefort, L.; Boogers, J. A. F.; de Vries, A. H. M; de Vries, J. G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2004**, *69*, 8045. (b) Yoshida, K.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2003**, *68*, 1901. (c) Kim, N.-J.; Moon, H.; Park, T.; Yun, H.; Jung, J.-W.; Chang, D.-J.; Kim, D.-D.; Suh, Y.-G. *J. Org. Chem.* **2010**, *75*, 7458.

(18) (a) Paquette, L. A.; Earle, M. J.; Smith, G. F. *Org. Synth.* **1996**, *73*, 36. (b) Kumar, R. J.; Chebib, M.; Hibbs, D. E.; Kim, H.-L.; Johnston, G. A. R.; Salam, N. K.; Hanrahan, J. R. *J. Med. Chem.* **2008**, *51*, 3825. (c) Curran, T. T.; Hay, D. A.; Koegel, C. P. *Tetrahedron* **1997**, *53*, 1983.

(19) (a) Ichikawa, M.; Takahashi, M.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2004**, *126*, 16553. (b) Soderquist, J. A.; Rivera, I.; Negron, A. *J. Org. Chem.* **1989**, *54*, 4051.

(20) Dupau, P.; Epple, R.; Thomas, A. A.; Fokin, V. V.; Sharpless, K. B. *Adv. Synth. Catal.* **2002**, *344*, 421.

(21) Schmidt, A. W.; Olpp, T.; Baum, E.; Stiffel, T.; Knölker, H.-J. *Org. Biomol. Chem.* **2010**, *8*, 4562.

(22) Birch, A. J.; Rao, S. *Tetrahedron Lett.* **1968**, *9*, 3797.

(23) For an example of competitive chelation of Lewis acids, see: Buckley, T. F.; Rapoport, H. *J. Am. Chem. Soc.* **1980**, *102*, 3056.

(24) Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, *23*, 4871.

(25) Pogrebnoi, S.; Saraber, F. C. E.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **2006**, *62*, 1743.

(26) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4464.

(27) We thank Dr. Saeed Khan of UCLA for the X-ray crystallographic data for **25** and **30**.

(28) Lee, E.; Yoon, C. H. *J. Chem. Soc., Chem. Commun.* **1994**, 479.

(29) (a) Jung, M. E.; Lyster, M. A. *J. Am. Chem. Soc.* **1977**, *99*, 968. (b) Jung, M. E.; Ornstein, P. L. *Tetrahedron Lett.* **1977**, *18*, 2659. (c) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761. (d) Jung, M. E.; Andrus, W. A.; Ornstein, P. L. *Tetrahedron Lett.* **1977**, *18*, 4175.

(30) For examples of similar results, see: (a) Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 1396. (b) Clark, R. D.; Heathcock, C. H. *Tetrahedron Lett.* **1974**, *15*, 2027. (c) Suryawanshi, S. N.; Fuchs, P. L. *J. Org. Chem.* **1986**, *51*, 902.