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Synthesis of Cardiotonic Steroids Oleandrigenin and Rhodexin B.

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Abstract

This article describes a concise synthesis of cardiotonic steroids oleandrigenin (**7**) and its subsequent elaboration into the natural product rhodexin B (**2**) from the readily available intermediate (**8**) that could be derived from the commercially available steroids testosterone or DHEA *via* three-step sequences. These studies feature an expedient installation of the β 16-oxidation based on β 14-hydroxyl-directed epoxidation and subsequent epoxide rearrangement. The following singlet oxygen oxidation of the C17 furan moiety provides access to oleandrigenin (**7**) in 12 steps (LLS) and a 3.1% overall yield from **8**. The synthetic oleandrigenin (**7**) was successfully glycosylated with 1-rhamnopyranoside-based donor **28** using a Pd(II)-catalyst, and the subsequent deprotection under acidic conditions provided cytotoxic natural product rhodexin B (**2**) in a 66% yield (two steps).

Graphical Abstract

Keywords

Cardiotonic Steroid; Total Synthesis; Natural Product; Oleandrigenin; Oleandrin; Rhodexin B; Glycosylation

1. Introduction

Cardiotonic steroids represent a broad family of natural steroids found in various plant and animal sources and featuring *cis*-CD (and often *cis*-AB) ring junction with β 14-hydroxylation and a 5- or 6-membered oxygenated heterocycle at the C17 position of

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Supporting Information

Experimental procedures, ¹H and ¹³C NMR spectra are available free of charge via the Internet.

the steroidal skeleton. These uniquely shaped steroids serve as potent inhibitors of Na⁺/K⁺-ATPase and, as a result, exhibit a great range of valuable physiological effects on humans and animals. (1) These effects include cardiotonic, (1) anticancer, (2) antiviral, (3) immunomodulatory, (4) and anti-inflammatory activities, (5) for which cardiotonic steroids have been used or evaluated as the potential therapeutic agents.

Among various cardiotonic steroids, cardenolide oleandrin (**1**) has received significant attention due to its rich biological profile. (6–8) This compound is isolated from the ornate shrub *Nerium oleander*, which is used in traditional medicine to treat various conditions including hemorrhoids, ulcers, and leprosy. The hot (Anvirzel) and cold (Breastin) extracts of *N. oleander* have been developed for the treatment of cancer. (7) Similarly, the supercritical CO₂ *N. oleander* extract PBI-05204 has been recently investigated in phase I and II clinical trials of patients with cancer in the United States and demonstrated *in vitro* and *in vivo* efficacies against various viruses including SARS-Cov-2. (8)

The principal active ingredient of these extracts, oleandrin (**1**), features β16-acetoxy-substitution and glycosylation with an unusual 2-deoxysugar, l-oleandrose (*cf.* Figure 1). It is noteworthy that its aglycone, oleandrigenin (**7**), is found in various bioactive natural products such as rhodexin B/tupichinolide (**2**) (9) and cryptostigmins I and II. It is also noteworthy that β16-variants of oleandrigenin (**7**) are also abundant in nature such as the formylation variant gitaloxin (**3**) or free hydroxyl gitoxin (**4**). Nevertheless, the availability of the β16-oxygenated cardenolides for medicinal chemistry exploration has been significantly limited by the lack of reliable synthetic routes to these steroids. While many recent studies have focused on developing concise approaches to cardiotonic steroids, (10,11) to date, there is only one reported synthesis of oleandrigenin (**7**) by Wicha and co-workers (*cf.* Scheme 1). (12) This synthesis relies on testosterone propionate as the starting material that is subsequently elaborated into oleandrigenin in 18 steps and features a late-stage C16 and C14 oxygenation installation.

Our group has long-standing interests in developing concise total syntheses of cardiotonic steroids and their analogues for the subsequent medicinal chemistry and chemical biology explorations. (13) Due to the intriguing biological profile exhibited by oleandrin (**1**) and other cardiotonic steroids derived from oleandrigenin (**7**), we were recently interested in developing the total synthesis of **7** and its glycosides. For the medicinal chemistry exploration of this compound, we targeted a synthetic route that would minimize the D-ring manipulations after the installation of the β17-substituent. We surmised that this could be accomplished if vinyl iodide **5** containing the preinstalled β14-OH group is used as the advanced intermediate. This compound could be conveniently converted to epoxide **6**, which, when subjected to a Lewis acid, undergoes epoxide rearrangement to install the desired β17 stereochemistry and oxygenation at the C16 position. (14) It is noteworthy that during the preparation of this manuscript, Inoue and co-workers applied a related rearrangement of an epoxide derived from **5** to the synthesis of bufadienolides; (15) however, no applications of this to the synthesis of cardenolides such as **7** have been described to date. Using this approach, we describe the development of the 15-step synthesis of oleandrigenin (**7**) from testosterone (or DHEA) and the subsequent elaboration of **7** into the glycosylated natural product rhodexin B (**2**), also known as tupichinolide. To the

best of our knowledge, this is the first successful example of the C3 sugar installation in the presence of the β 16-acetoxy group, and we believe that the studies described in this manuscript will be instrumental for the future medicinal chemistry exploration of glycosylated oleandrogenin (**7**) derivatives.

2. Results and Discussion

Our synthetic studies commenced with the known steroid derivative **8** that could be generated from DHEA (three steps, 38% yield) or testosterone (three steps, 76% yield). This derivative was subjected to D-ring modification by first installing an enone through Saegusa–Ito's two-step oxidation in a 65% yield. Taking advantage of the torsional strain of the C- and D-rings due to the unsaturation at (15)-alkene, the deconjugation was accomplished using our group's previously developed conditions (PhMe, SiO₂, DIEA, 60 °C) to produce the β,γ -unsaturated ketone **9** in a 69% yield (95% bsrn). The subsequent studies were focused on installing the β 14-hydroxyl group *via* Mukaiyama hydration (16) (*cf.* Table 1) using the 5 α -isomeric compound **10** as the model system. The standard conditions involving Co(acac)₂ (17 mol %), phenyl silane, and O₂ in 1,4-dioxane at rt yielded β -product **11** and its α -diastereomer **12** as an inseparable 1.5:1 mixture (entry 1). In our attempts to optimize the dr of this reaction, we subsequently investigated Magnus' variant (17) of Mukaiyama hydration (entry 2). As before, this hydration reaction proceeded efficiently; however, the observed **11**:**12** selectivity dropped to 1:1. The preference for β 14-OH is due to the higher stability of the C₁₄radical *cis*-hydrindane intermediate, and, with this regard, conditions in entries 1 and 2 are equivalent as both sets of conditions employ dioxygen for trapping. Arguing that a larger trapping agent may result in a better β 14-selectivity, we examined anaerobic conditions by Studer (entry 3). (18) These conditions indeed resulted in the improved β/α selectivity ($\beta/\alpha = 10:1$); however, despite the complete conversion, product **11** was isolated in only a 37% yield. This low yield was attributed to the formation of the hydroxylamine and other polar side products observed in the Studer studies. (18) Considering that this did not represent an improvement to the yield previously reported by the Inoue group, (15) the classical Mukaiyama hydration conditions were selected moving forward (*cf.* Scheme 2). Thus, our subsequent studies focused on using Co(acac)₂/PhSiH₃/O₂ conditions developed above and the hydration of **9** was carried out on a 1.2 g scale providing the mixture of epimers at the C14 position (14 β /14 $\alpha = 2.9:1$). The resultant product was subjected to the Barton procedure to provide the known vinyl iodide **5** in a 38% yield from **9**. Vinyl iodide **5** represents an important intermediate for the further functionalization of the C17 position, and its subsequent Suzuki cross-coupling with the commercially available boronic acid **13** proceeded in a 76% yield. The resultant intermediate was subjected to β 14-hydroxyl-directed epoxidation with *m*CPBA to afford epoxide **6** in good yield and excellent diastereoselectivity (77%, >20:1 dr). Similarly, **5** underwent Stille cross-coupling with the commercially available stannane **14** (42% yield, 80% BRSM), and subsequent β 14-hydroxyl-directed epoxidation under the Sharpless conditions provided epoxide **15** (70% yield, >20:1 dr). With epoxides **6** and **15** in hand, our subsequent efforts were focused on identifying the best conditions to accomplish the epoxide rearrangement resulting in the installation of the C17 stereocenter and C16 ketone (*cf.* Scheme 3). Our studies commenced by subjecting α 5-isomer of **6**,

compound **16**, to the known conditions (BF₃·Et₂O, DCM, −78 °C, 30 min) (**14**) that indeed resulted in the formation of the desired rearrangement product **17** (45% yield) along with multiple decomposition products. Surmising that **17** might not be stable to Lewis acids, we investigated the possibility of a single-step rearrangement followed by the C16 ketone reduction. The inclusion of triethylsilane to the aforementioned conditions provided the corresponding reduction product **18** (38% yield) in addition to **17** (19% yield). Our subsequent attempts to improve the formation of **18** by varying the temperature, Lewis acids, or silane source did not lead to the improvement in yield. However, these optimization studies led to the realization that more Lewis basic solvents such as 1,4-dioxane or THF may significantly improve the formation of **17**. Thus, the formation of **17** was significantly increased (93% yield) by altering the solvent, temperature, and reaction time (BF₃·Et₂O, dioxane, rt, 1 min). These optimized conditions were subsequently applied for the isomerization of butenolide-containing epoxide **15** (*cf.* Scheme 3); however, both **15** and its rearrangement products were found to be unstable to Lewis acids, and our attempts to directly produce **19** from **15** were not successful. While it is known that similar cardenolide epoxides may undergo various skeletal rearrangements under the Lewis acidic conditions, (19) the observations made by the Inoue group in their studies of the related rearrangement of bufadienolides (**15**) suggest that further optimization of the Lewis acid and the reaction conditions may result in the productive formation of **23**.

The optimized conditions used for the model studies leading to **17** were subsequently used to promote the isomerization of epoxide **6** containing the desired 5β-configuration (*cf.* Scheme 4). This transformation proceeded in a 95% yield and provided **21** as the single diastereomer. Most importantly, the analysis of this compound, as well as the subsequent intermediates, was consistent with the stereoselective hydrogen migration in intermediate **20** to establish the desired β17-stereocenter. Thus, the obtained ketone **21** was subjected to the reduction with NaBH₄ to provide the desired β16-product in a 76% yield and 9.6:1 d.r. The resultant diastereomeric mixture was separated by normal phase column chromatography, and the desired diastereomer was acylated (Ac₂O, DMAP, Py) to provide the known intermediate **22** as a single diastereomer after purification. The conversion of **22** into oleandrigenin (**7**) was subsequently carried out using the previously published protocol from the Wicha group, which involved singlet oxygen to oxidize the furan moiety, followed by the reductive rearrangement and acidic workup leading to the formation of β17-butenolide (51% yield) along with deprotected oleandrigenin (10% yield). (12c) The subsequent HF·Py-mediated deprotection of the TBS group completed the formation of oleandrigenin (**7**) from **22** in 56% over 2 steps (12 linear steps and 3.1% yield from **8**). Importantly, the spectroscopic data obtained for **7** well matched the corresponding characterization data previously disclosed by the Wicha group, (12c) thus confirming the identity of synthetic oleandrigenin (**7**).

With the concise approach to **7** in hand, our subsequent studies focused on developing a strategy for the C3 glycosylation leading to rhodexin B (**2**) containing α-l-rhamnose at the C3 position (*cf.* Scheme 5). While the chemical glycosylation of cardiotonic steroids has been previously accomplished in various contexts (11a,b,g) including our own studies, (13c,e,f) to the best of our knowledge, the glycosylation of **7** has not been previously

investigated. The β 16-acetate moiety presents additional challenges for the introduction of sugar. When aglycone **7** was subjected to the standard glycosylation conditions with the known donor **23**, (13c,e,f) glycosylated product **24** was indeed obtained in good yield and selectivity (60%, 10:1 dr) along with the minor quantities of the C14-elimination side product (~5% yield). However, accomplishing a selective deprotection of the benzoates on l-rhamnose moiety of **24** represented a major challenge as the use of various basic conditions invariably leads to the deprotection of the β 16-acetate group before the benzoate moieties were completely removed. While we were not able to isolate any partially deprotected intermediates, we surmised that the rates for the cleavage of the C2'-benzoate and β 16-acetate groups are similar under the weakly basic conditions. Previously, our group encountered a related problem in the context of accomplishing a selective deprotection of the C19-position of cannogenol- α -l-rhamnoside, (13c) and the challenges associated with the selective deprotection of the C19-position in the presence of butenolide were solved by employing 2-methoxyacetate (MAc)-protecting group that is significantly more labile than benzoate under both acidic and basic conditions. (20) Based on these considerations, the reaction of **7** and MAc-protected l-rhamnose trichloroacetimidate **25** (21) was accomplished to provide α -l-rhamnoside **26** in an 87% yield as the only observable isomer. As before, minor amounts of the β 14-hydroxide elimination accompanied the formation of **26**. Glycoside **26** was then subjected to various basic and Lewis acidic conditions; however, the challenges with the carbohydrate moiety deprotection still persisted. Thus, the treatment of **26** with the saturated solution of NH_3 in MeOH led to the selective formation of the monoprotected glycoside **27** still containing MAc protection at the 2'-position of the l-rhamnose moiety. Further exposure of **27** to the ammonia in methanol led to the competitive cleavage of the β 16-acetate and subsequent degradation of butenolide and did not result in rhodexin B. Similarly, exposure of **27** to $\text{Yb}(\text{OTf})_3$ (50 mol %) in methanol, the conditions previously used to effectively cleave MAc groups, (20b) resulted in the cleavage of the glycosidic linkage and β 14-hydroxide elimination. Based on these observations, a different trichloroacetimidate donor **28** previously developed by Nguyen and co-workers was investigated next (Scheme 6). (22) The reaction of **28** and **7** was first attempted using the previously developed conditions employing TMSOTf (10 mol %) as the catalyst; however, an ~ 1:1 ratio of the desired glycoside **29** and the β 14-hydroxide elimination side product **30** was observed under these conditions. In attempts to optimize the formation of **30**, the conditions were developed by the Nguyen group (22) for the glycosylation with **28** and employing $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ (10 mol %) as the catalyst. While at room temperature this reaction led to the formation of **30** as the major product, at -78°C , this reaction resulted in **29** (76% yield, >20:1 dr) along with **30** (ca. 15% yield, > 20:1 dr). Desired product **29** was successfully separated from **30** and subjected to deprotection using HCl in methanol. These conditions provided a synthetic sample of rhodexin B(**2**) (87% yield). The subsequent comparison of the spectroscopic characteristics of the synthetic sample provided a good match with the published ^1H , ^{13}C NMR, and optical rotation data (9c)(*cf.* Supporting Information).

3. Conclusions

In conclusion, this article describes a new concise synthesis of valuable cardiotonic steroid oleandrin (7) from a readily available derivative of DHEA or testosterone (8) and its subsequent elaboration into natural product rhodexin B/tupichinolide (2). This synthesis features Lewis acid-catalyzed epoxide rearrangement of a precursor with preinstalled β 14-hydroxylation. This strategy allowed us to achieve a more concise reaction sequence leading to 7 (12 steps, 3.1%) from 8 and avoid synthetic manipulations on the late-stage intermediates containing the β 17-substitution. We have evaluated various protecting group strategies for the installation of the α -l-rhamnoside and established a viable route that could be used to produce natural product rhodexin B(2) and its analogues for the biological evaluation. We believe that these studies are instrumental for the synthesis of oleandrin (1) and other steroids bearing the β 16-oxidation, and our future studies will be focused on expanding this work to generate such natural products and their analogues for the medicinal chemistry explorations. (23)

4. Experimental Section

4.1. General Methods

All reagents and solvents were purchased from commercial sources and used as received without further purification unless otherwise specified. DCM, DMF, Et₂O, THF, and PhMe were purified by Innovative Technology's Pure-Solve System using basic alumina. All reactions were carried out under a positive pressure of nitrogen in flame- or oven-dried glassware with magnetic stirring. Reactions were cooled using a cryocooler or external cooling baths (ice water (0 °C), sodium chloride/ice water (−20 °C), dry ice/acetonitrile (−40 °C), or dry ice/acetone (−78 °C)). Heating was achieved by use of a silicone oil bath, with heating controlled by an electronic contact thermometer. Deionized water was used in the preparation of all aqueous solutions and for all aqueous extractions. Solvents used for extraction and chromatography were of ACS or HPLC grade. Purification of reaction mixtures was performed by flash chromatography using SiliCycle SiliaFlash P60 (230–400 mesh). Yields indicate the isolated yield of the title compound with 95% purity as determined by ¹H NMR analysis. Diastereomeric ratios were determined by ¹H NMR analysis. ¹H NMR spectra were recorded on a Varian vnmrs 700 (700 MHz), 600 (600 MHz), 500 (500 MHz), 400 (400 MHz), Varian Inova 500 (500 MHz), or a Bruker Avance Neo 500 (500 MHz) spectrometer, and chemical shifts (δ) are reported in parts per million (ppm) with solvent resonance as the internal standard (CDCl₃ at δ 7.26, D₃COD at δ 3.31, C₆D₆ at δ 7.16). Tabulated ¹H NMR data are reported as s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, m = multiplet, ovrlp = overlap, and coupling constants in Hz. Proton-decoupled ¹³C NMR spectra were recorded on a Varian vnmrs 700 (700 MHz) spectrometer, and chemical shifts (δ) are reported in ppm with solvent resonance as the internal standard (CDCl₃ at δ 77.16, D₃COD at δ 49.0, C₆D₆ at δ 128.06). High-resolution mass spectra (HRMS) were performed and recorded on Micromass AutoSpec Ultima or VG (Micromass) 70–250-S Magnetic sector mass spectrometers in the University of Michigan mass spectrometry laboratory. Infrared (IR) spectra were recorded as thin films on a Perkin Elmer Spectrum BX FT-IR spectrometer. Absorption peaks are

reported in wavenumbers (cm^{-1}). Optical rotations were measured at room temperature in CHCl_3 or H_3COH on a Jasco P-2000 polarimeter.

5. Synthesis of Substrate 8 (DHEA Route)

5.1. Structure 8a

Using a modification of the previously reported method, (24a) DHEA was converted to **8a** as follows: DHEA (25.0 g, 86.7 mmol) and cyclohexanone (20.0 eq, 180 mL, 1.73 mole) were added to a flame-dried 1 L round-bottom flask. The flask was connected to a condenser and flushed with N_2 prior to charging the flask with PhMe (0.17 M, 500 mL). The solution was stirred and heated to reflux for 15 min and then charged with aluminum isopropoxide ($\text{Al}(\text{O}i\text{Pr})_3$, 2.5 equiv, 44.3 g, 217 mmol), creating a clear yellow solution. The reaction was stirred for 30 min at reflux before turning off the heat and cooled to room temperature. The reaction was washed with 3 N HCl (100 mL $\times$ 3), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was recrystallized with EtOAc three times to give known compound **8a** (21.3 g, 74.4 mmol) in an 86% yield. The mother liquor was purified by flash column chromatography on silica gel (hexane/EtOAc = 4:1) to afford the remaining **8a** (2.25 g, 7.86 mmol) for a total yield of 95% yield as a white crystalline solid. R_f 0.50 in 1:1 hexane/EtOAc ^1H NMR (700 MHz, CDCl_3): δ 5.75 (s, 1H), 2.52–2.29 (m, 5H), 2.18–2.04 (m, 1H), 2.08–1.98 (m, 1H), 1.97 (td, J = 8.4, 7.2, 4.2 Hz, 2H), 1.86 (dt, J = 13.1, 3.6 Hz, 1H), 1.71 (ddd, J = 18.1, 13.4, 7.2 Hz, 3H), 1.63–1.51 (m, 1H), 1.46 (qd, J = 12.9, 4.0 Hz, 1H), 1.29 (tt, J = 13.1, 6.8 Hz, 2H), 1.21 (s, 3H), 1.17–1.06 (m, 1H), 0.99 (td, J = 11.6, 4.1 Hz, 1H), 0.92 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3): δ 220.4, 199.4, 170.4, 124.3, 53.9, 51.0, 47.6, 38.7, 35.8, 35.8, 35.3, 34.0, 32.7, 31.4, 30.9, 21.9, 20.4, 17.5, 13.8.

5.2. Structure 8b

Using a modification of the previously reported method (24a), **8a** was converted to **8b** as follows: **8a** (21.3 g, 74.4 mmol) and Pd/C (5 mol %, 10 w/w % Pd on carbon, 4.17 g, 3.92 mmol) were added to a flame-dried 2 L round-bottom flask. The flask was flushed with N_2 , and anhydrous pyridine (0.1 M, 745 mL) was added to the flask to give a black suspension. The flask was flushed with H_2 , and the suspension was left to stir under a H_2 atmosphere (1 atm) at room temperature for 14 hours. The suspension was filtered through a pad of celite with EtOAc (250 mL) and concentrated *in vacuo*. The crude oil was dissolved in EtOAc (500 mL) and washed with 10 w/v % CuSO_4 (50 mL), saturated aqueous NH_4Cl (100 mL $\times$ 2), and then brine (200 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was recrystallized from hexane to give **8b** (9.88 g, 34.3 mmol) as a single diastereomer in a 46% yield as a white solid. R_f 0.48 in 1:1 hexane/EtOAc. Mp 120–123 $^\circ\text{C}$ $[\alpha]_{\text{D}}^{27}$ = +72.8 (c = 0.27, CHCl_3). IR (thin film): 2929, 2860, 1735, 1712, 1653 cm^{-1} . ^1H NMR (700 MHz, CDCl_3): δ 2.68 (t, 1H), 2.47 (dd, J = 19.2, 8.8 Hz, 1H), 2.32 (td, J = 14.6, 5.4 Hz, 1H), 2.22–2.16 (m, 1H), 2.16–1.90 (m, 4H), 1.90–1.82 (m, 3H), 1.75–1.57 (m, 3H), 1.55–1.35 (m, 2H), 1.37–1.33 (m, 3H), 1.35–1.13 (m, 2H), 1.05 (s, 3H), 0.89 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3): δ 220.9, 212.9, 51.5, 48.0, 44.3, 42.4, 41.2, 37.3, 37.1, 36.0, 35.3, 35.2, 31.8, 26.5, 24.9, 22.7, 21.9, 20.6, 13.9. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{28}\text{O}_2\text{Na}$ 311.1987; found 311.1977.

5.3 Structure 8

Diketone **8b** was added to a flame-dried 500 mL round-bottom flask (3.20 g, 11.1 mmol). The flask was flushed with N₂ before dissolving the solid in anhydrous THF (110 mL) and cooled to –78 °C. *K*-Selectride (1.5 equiv, 1.0 M THF solution, 22.1 mL, 22.2 mmol) was added to the solution dropwise and monitored by TLC until starting material was consumed (50% hexane/EtOAc, 30 min). Once the starting material was consumed, dimethylformamide (110 mL) was added to the solution at –78 °C. Imidazole (4.0 equiv, 3.01 g, 44.3 mmol) and then *tert*-butyldimethylsilyl chloride (3.0 equiv, 5.01 g, 33.2 mmol) were added to the solution. The reaction was warmed to room temperature and stirred for 16 h while concentrating over a stream of N₂. The reaction was then concentrated *in vacuo* and brought up in EtOAc (500 mL) and washed with ice-cold 50% brine/deionized water (300 mL × 4) and then brine (300 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 1:0 to 24:1 to 9:1) to afford **8** (3.97 g, 9.81 mmol) as a single diastereomer in an 88% yield as a white solid. *R*_f 0.63 in 9:1 hexane/EtOAc. Mp 123–125 °C [α]_D²⁷ = +53.5 (*c* = 0.31, CHCl₃). IR (thin film): 2926, 2856, 1740 cm^{–1}. ¹H NMR (700 MHz, CDCl₃): δ 4.03 (t, *J* = 2.8 Hz, 1H), 2.43 (dd, *J* = 19.3, 8.9 Hz, 1H), 2.06 (dt, *J* = 18.8, 9.1 Hz, 1H), 1.91 (dddd, *J* = 18.1, 13.7, 8.7, 5.1 Hz, 2H), 1.87–1.78 (m, 3H), 1.62–1.15 (m, 16H), 1.11 (qd, *J* = 13.2, 4.2 Hz, 1H), 0.96 (s, 3H), 0.88 (s, 9H), 0.85 (s, 3H), 0.01 (s, 6H). ¹³C{¹H} NMR (176 MHz, CDCl₃): δ 221.7, 67.4, 51.8, 48.1, 40.4, 36.7, 36.1, 35.5, 35.4, 34.5, 32.0, 30.2, 28.7, 26.8, 26.0, 25.6, 24.1, 22.0, 20.5, 18.2, 14.0, –4.7. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₂₅H₄₄O₂SiNa 427.3008; found 427.3002.

6. Synthesis of Substrate 9

6.1. Substrate 9a

In a flame-dried 100 mL round-bottom flask, diisopropylamine (1.5 equiv, 1.8 mL, 13.1 mmol) was added to THF (0.66 M, 20 mL) and then cooled to –78 °C under a N₂ atmosphere. Freshly titrated *n*-BuLi (1.5 equiv, 2.45 M, 13.1 mmol, 5.35 mL) was added to the solution dropwise. The solution was warmed to 0 °C on an ice bath for 30 min before cooling back down to –78 °C. A solution of **8** (1.0 equiv, 3.53 g, 8.72 mmol) in THF (0.67 M, 13.0 mL) was cooled to –78 °C before adding to the solution of LDA dropwise. The reaction mixture was stirred at –78 °C for 30 min. The flask was charged with TMSCl (1.5 equiv, 1.65 mL, 13.1 mmol) and stirred for 1 h as the reaction warmed to room temperature. The reaction was quenched with ice-cold NaHCO₃(sat) and then extracted with pentane (35 mL × 4). The organic layer was dried over Na₂SO₄, filtered, and concentrated to afford the crude silyl enol ether, which was used in the next reaction without further purification. Pd(OAc)₂ (1.1 equiv, 2.16 g, 9.59 mmol) was added to a solution of the above crude silyl enol ether in CH₃CN (0.2 M, 44 mL) at room temperature. After the reaction mixture was stirred at room temperature for 12 h, the suspension was filtered through a pad of celite with EtOAc (100 mL) and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc = 24:1) to afford enone **9a** (2.27 g, 5.64 mmol) in a 65% yield as a white solid. *R*_f 0.40 in 9:1 hexanes/EtOAc. Mp 151–154 °C. [α]_D²⁷ –24.2 (*c* = 0.23, CHCl₃). IR (film, cm^{–1}) 3346, 2928, 2855, 1710, 1561 cm^{–1}. ¹H NMR (700 MHz, CDCl₃) δ 7.53–7.50 (m, 1H), 6.01 (dd, *J* = 6.0, 3.0 Hz, 1H), 4.04 (s, 1H), 2.33 (dt, *J*

= 11.3, 2.5 Hz, 1H), 1.99–1.92 (m, 1H), 1.90–1.78 (m, 4H), 1.75–1.70 (m, 1H), 1.62–1.35 (m, 10H), 1.28–1.18 (m, 3H), 1.05 (s, 3H), 1.00 (d, $J = 1.6$ Hz, 3H), 0.89 (d, $J = 1.6$ Hz, 9H), 0.02 (d, $J = 1.6$ Hz, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3): δ 213.7, 158.9, 131.8, 67.3, 57.4, 51.4, 41.8, 36.7, 35.6, 34.6, 32.9, 30.1, 29.6, 28.7, 26.7, 26.0, 25.6, 24.1, 20.9, 20.2, 18.2, –4.7. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$: calcd for $\text{C}_{25}\text{H}_{43}\text{O}_2\text{Si}$ 403.3027; found 403.3015.

6.2. Substrate 9

i-Pr₂EtN (10.0 equiv, 8.5 mL, 48.9 mmol) was added to a suspension of enone **9a** (1.97 g, 4.89 mmol) and SiO₂ (6.0 equiv, 1.76 g, 29.4 mmol) in toluene (0.1 M, 50 mL) at room temperature. The reaction was warmed to 60 °C and stirred for 7 h. The reaction was diluted with EtOAc (100 mL), filtered, and then washed with 1 N HCl (30 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (hexanes/EtOAc = 1:0 to 24:1 to 9:1) to afford **9** (1.35 g, 3.35 mmol) and enone **9a** (515 mg, 1.28 mmol) in a 69% yield and 95% BRSM, respectively, as white solids. R_f : 0.63 in 9:1 hexanes/EtOAc. Mp 109–111 °C. $[\alpha]_D^{27} +75.4$ ($c = 0.34$, CHCl_3). IR (film, cm^{-1}) 2925, 2882, 2859, 1738, 1639. ^1H NMR (700 MHz, CDCl_3) δ 5.48 (d, $J = 2.5$ Hz, 1H), 4.01 (t, $J = 2.6$ Hz, 1H), 2.99 (ddd, $J = 23.1, 4.1, 1.7$ Hz, 1H), 2.83 (dt, $J = 23.0, 2.3$ Hz, 1H), 2.18 (t, $J = 11.1$ Hz, 1H), 1.96 (tt, $J = 13.9, 4.2$ Hz, 1H), 1.86–1.74 (m, 3H), 1.62–1.49 (m, 5H), 1.45–1.32 (m, 5H), 1.23 (ddd, $J = 19.5, 9.6, 3.5$ Hz, 3H), 1.10 (s, 3H), 0.99 (s, 3H), 0.88 (s, 9H), 0.01 (s, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3) δ 223.0, 154.3, 112.7, 67.4, 51.2, 41.6, 41.3, 36.6, 35.8, 35.6, 34.4, 33.7, 29.9, 28.8, 26.5, 26.0, 23.8, 23.2, 21.0, 20.1, 18.2, –4.7, –4.7. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{43}\text{O}_2\text{Si}$ 403.3027; found 403.3024.

7. Synthesis of 5 from 9

7.1. Substrate 5a

A solution of **9** (1.19 g, 2.95 mmol) and cobalt(II) acetylacetonate ($\text{Co}(\text{acac})_2$, 0.2 equiv, 152 mg, 0.59 mmol) in 1,4-dioxane (30 mL) was bubbled with O₂ for 10 min at room temperature. A solution of PhSiH₃ (3.1 equiv, 1.1 mL, 9.0 mmol) in 1,4-dioxane (5.5 mL) was added to the mixture at room temperature over 2 h *via* a syringe pump under an O₂ atmosphere (1 atm). After the reaction mixture was stirred under an O₂ atmosphere (1 atm) at room temperature for 3 hours, saturated aqueous NaHCO₃ (10 mL) and 10 w/v % Na₂S₂O₃ were added to the mixture. The resultant mixture was extracted with CH₂Cl₂ (50 mL $\times$ 4). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was passed through a silica gel plug (hexane/EtOAc = 1:1) to afford a 2.9:1 mixture of two C14-epimeric alcohols β -**5a** and α -**5a** as a gel. The gel was used in the next reaction without further purification.

7.2. Substrate 5

Hydrazine monohydrate (N₂H₄·H₂O, 17.5 equiv, 2.5 mL, 51.5 mmol) was added to a solution of the alcohols β -**5a** and α -**5a** from above and Et₃N (17.6 equiv, 7.3 mL, 52.0 mmol) in absolute ethanol (130 mL). The reaction flask was flushed with N₂ and heated to 50 °C for 12 h and then concentrated *in vacuo* to white crystals. The flask was removed

from high vacuum and flushed with N₂ before adding Et₃N (20.0 equiv, 7.3 mL, 52.0 mmol) and dissolving in THF (130 mL). The reaction was stirred vigorously at room temperature as a solution of I₂ (3.5 equiv, 2.6 g, 10.3 mmol) dissolved in THF (5 mL) was added dropwise until the solution turned brown. The reaction was stirred for 10 min until the solution returned to a yellow color before adding more of the I₂ solution until the brown color persisted. The reaction was stirred for 1 h at room temperature and then quenched with 10 w/v % Na₂S₂O₃ (100 mL). The mixture was diluted with deionized water (500 mL) and then extracted with CH₂Cl₂ (200 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on F60 silica gel (hexanes/EtOAc = 49:1 to 24:1 to 9:1) to afford vinyl iodide **5** (601 mg, 1.13 mmol) in a 38% yield over two steps as a white solid. The identity was confirmed by comparison to the previously reported variant. (15)*R*_f 0.49 in 9:1 hexanes/EtOAc. Mp 123–125 °C. [α]_D²⁷ +14.3 (*c* = 0.29, CHCl₃). IR (film, cm⁻¹): 3444, 2928, 2884, 2857. ¹H NMR (700 MHz, CDCl₃) δ 6.11 (t, *J* = 2.5 Hz, 1H), 4.04 (d, *J* = 3.7 Hz, 1H), 2.56 (dd, *J* = 16.4, 1.9 Hz, 1H), 2.21 (dd, *J* = 16.4, 3.2 Hz, 1H), 1.88 (td, *J* = 14.5, 7.4 Hz, 1H), 1.84–1.74 (m, 4H), 1.65 (td, *J* = 11.9, 3.8 Hz, 1H), 1.56–1.40 (m, 5H), 1.37 (dt, *J* = 13.2, 3.3 Hz, 1H), 1.27–1.15 (m, 4H), 1.04 (s, 3H), 1.04–0.98 (m, 1H), 1.01–0.95 (m, 1H), 0.94 (s, 3H), 0.88 (s, 9H), 0.02 (s, 6H). ¹³C{¹H} NMR (176 MHz, CDCl₃) δ 133.7, 111.6, 82.7, 67.3, 55.0, 42.8, 41.6, 37.7, 36.7, 36.2, 35.4, 34.4, 29.9, 28.9, 26.7, 26.0, 24.2, 21.3, 19.9, 18.2, 18.1, –4.7, –4.7. HRMS (ESI-TOF) *m/z*: [M – H₂O – C₆H₁₅Osi]⁺ calcd for C₁₉H₂₆I 381.1074; found 381.1068.

8. Synthesis of **6** from **5**

8.1. Substrate **6a**

Substrate **5** (862 mg, 1.62 mmol) and 3-furanylboronic acid **13** (544 mg, 4.86 mmol, 3.0 equiv) were transferred to a flame-dried round-bottom flask with a magnetic stir bar. The flask was then transferred to a glovebox where PdCl₂(PPh₃)₄ (0.10 equiv, 187 mg, 0.16 mmol) was weighed out into the reaction flask. Afterward, the flask was taken out of the glovebox and dry toluene (20 mL) was introduced, followed by MeOH (4 mL) and NaHCO₃(sat.) (4 mL). The biphasic suspension was then equipped with a reflux condenser and heated to 80 °C from an oil bath while stirring for 18 h. After the designated reaction time, the heat was turned off and the flask was allowed to cool to room temperature. Then, the reaction solution was partitioned between DI water (20 mL) and a 1:1 mixture of EtOAc/hexanes (20 mL). The layers were separated, and the organic phase was washed with HCl (1 N aq. solution, 30 mL), H₂O (30 mL), and then brine (30 mL). The organic phase was then dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Flash column chromatography was performed on the crude residue through silica gel (hexanes/EtOAc = 9:1) to afford **6a** (579 mg, 1.23 mmol) in a 76% yield as a white solid. *R*_f 0.39 in 9:1 hexanes/EtOAc. Mp 125–128 °C. [α]_D²⁷ +41 (*c* = 0.05, CHCl₃). IR (film, cm⁻¹) 3446, 2942, 2855, 2361, 2339. ¹H NMR (500 MHz, CDCl₃) δ 7.44 (s, 1H), 7.36 (t, *J* = 1.6 Hz, 1H), 6.47 (dd, *J* = 1.9, 0.9 Hz, 1H), 5.75 (t, *J* = 2.5 Hz, 1H), 4.05 (t, *J* = 2.8 Hz, 1H), 2.69 (dd, *J* = 17.0, 2.0 Hz, 1H), 2.25 (dd, *J* = 17.1, 3.2 Hz, 1H), 1.97 (dt, *J* = 13.1, 3.0 Hz, 1H), 1.92 (t, *J* = 4.4 Hz, 1H), 1.89 (d, *J* = 2.7 Hz, 1H), 1.86 (d, *J* = 2.4 Hz, 1H), 1.85–1.79 (m, 2H), 1.72 (ddd, *J* = 15.6, 9.9, 3.9 Hz, 2H), 1.58 (dd, *J* = 11.6, 3.3 Hz, 1H), 1.55–1.48 (m, 2H), 1.48–1.45 (m, 1H),

1.43 (q, J = 3.4 Hz, 1H), 1.41–1.33 (m, 1H), 1.30–1.23 (m, 2H), 1.20–1.05 (m, 2H), 0.96 (s, 3H), 0.89 (s, 10H), 0.02 (s, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3) δ 144.1, 142.7, 138.3, 121.5, 121.2, 110.0, 86.0, 67.4, 52.3, 40.5, 40.1, 38.8, 36.5, 36.3, 35.4, 34.5, 30.0, 28.9, 26.8, 26.0, 24.2, 21.5, 20.1, 18.3, 17.0, –4.7, –4.7. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{29}\text{H}_{46}\text{O}_3\text{SiNa}$ 493.3108; found 493.3111.

8.2. Substrate 6

Intermediate **6a** from above (374 mg, 0.794 mmol) was dissolved in dry DCM (20 mL) in a flame-dried round-bottom flask with a magnetic stirring bar, and the reaction vessel was cooled to $-40\text{ }^\circ\text{C}$ in a dry ice/acetonitrile bath. Then, NaHCO_3 (1.20 equiv, 100 mg, 1.19 mmol) was added to the reaction, followed by *m*CPBA (75% w/w, 1.2 equiv, 241 mg, 0.979 mmol) after a 10 min incubation period. The reaction was then stirred for 5 h while warming but not reaching above $-10\text{ }^\circ\text{C}$. After the designated reaction time, the reaction was quenched with $\text{Na}_2\text{S}_2\text{O}_3(\text{sat})$ (20 mL) and then the cooling bath was removed. The solution was then vigorously stirred for 30 mins at room temperature to create a cloudy mixture. Then, the reaction solution was extracted with DCM ($3 \times 20\text{ mL}$) and EtOAc ($3 \times 20\text{ mL}$). The organic phase was washed with sat. Aq. NaHCO_3 (50 mL) and then brine (50 mL). The organic phase was then dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Flash column chromatography was performed on the crude solid through silica gel (hexanes/EtOAc = 19:1 to 9:1 to 4:1) to afford **6** (299 mg, 0.615 mmol) in an 77% yield as a white solid. R_f : 0.69 in 4:1 hexanes/EtOAc. Mp $154\text{--}157\text{ }^\circ\text{C}$. $[\alpha]_{\text{D}}^{27} +7.6$ (c = 0.13, CHCl_3). IR (film, cm^{-1}): 3357, 2926, 2854, 2361, 2338. ^1H NMR (400 MHz, C_6D_6) δ 7.25 (s, 1H), 7.06 (d, J = 1.5 Hz, 1H), 6.24 (d, J = 1.8 Hz, 1H), 4.08 (s, 1H), 3.57 (s, 1H), 3.30 (s, 1H), 2.18 (dd, J = 13.8, 3.5 Hz, 1H), 1.96–1.87 (m, 2H), 1.86–1.77 (m, 2H), 1.75–1.71 (m, 2H), 1.68 (dt, J = 10.9, 4.3 Hz, 2H), 1.52–1.46 (m, 2H), 1.41 (d, J = 16.8 Hz, 1H), 1.36 (t, J = 3.2 Hz, 1H), 1.31 (d, J = 3.5 Hz, 1H), 1.28–1.20 (m, 4H), 1.18 (s, 3H), 1.12 (dd, J = 13.1, 4.1 Hz, 1H), 1.02 (s, 9H), 0.94 (d, J = 14.6 Hz, 1H), 0.89 (s, 3H), 0.86–0.76 (m, 1H), 0.11 (d, J = 2.3 Hz, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, C_6D_6) δ 142.9, 141.6, 128.3, 120.1, 110.9, 80.9, 69.7, 67.9, 62.3, 46.7, 41.0, 36.6, 35.9, 35.5, 35.4, 35.1, 34.7, 30.2, 30.2, 29.2, 27.1, 26.1, 24.3, 21.6, 20.4, 18.4, 14.3, 1.4, –4.6, –4.6, –4.6. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{29}\text{H}_{46}\text{O}_4\text{SiNa}$ 509.3058; found: 509.3054.

9. Synthesis of 22 from 6

9.1. Substrate 21

Compound **6** from above (267 mg, 0.548 mmol) was dissolved in anhydrous 1,4-dioxane (27.5 mL) in a flame-dried round-bottom flask. Then, a solution of $\text{BF}_3 \cdot \text{OEt}_2$ (750 μL of a solution of 200 μL of $\text{BF}_3 \cdot \text{Oet}_2$ in 3 mL of dry Et_2O) was added to the reaction in quick drops. The reaction went from opaque to orange-brown and then transparent over the course of a minute. After such time, the solution was diluted with Et_2O (15 mL) and then quenched with $\text{NaHCO}_3(\text{sat.})$ (15 mL). The aqueous phase was extracted with DCM ($4 \times 20\text{ mL}$). The organic layer was then washed with brine (30 mL), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc = 19:1 to 9:1) to afford **21** (253 mg, 0.519 mmol) in a 95% yield as a white solid. R_f : 0.5 in 4:1 hexanes/EtOAc. Mp $143\text{--}147\text{ }^\circ\text{C}$. $[\alpha]_{\text{D}}^{27} +67.1$ (c = 0.06, CHCl_3).

IR (film, cm^{-1}): 3454, 2930, 2856, 2365, 2341. ^1H NMR (700 MHz, CDCl_3) δ 7.33 (d, J = 1.9 Hz, 1H), 7.26 (overlapping with CDCl_3 s, 1H), 6.36 (d, J = 1.7 Hz, 1H), 4.06 (t, J = 2.8 Hz, 1H), 3.05 (s, 1H), 2.83 (d, J = 18.2 Hz, 1H), 2.33 (d, J = 18.2 Hz, 1H), 1.87 (td, J = 13.8, 6.9 Hz, 1H), 1.83 (d, J = 14.1 Hz, 1H), 1.79–1.73 (m, 3H), 1.68 (td, J = 12.0, 3.7 Hz, 1H), 1.62–1.57 (m, 2H), 1.54 (td, J = 14.2, 3.7 Hz, 2H), 1.45 (qd, J = 11.4, 9.3, 3.7 Hz, 3H), 1.40 (d, J = 9.2 Hz, 2H), 1.31 (qd, J = 13.3, 3.5 Hz, 1H), 1.27–1.21 (m, 4H), 1.13 (qd, J = 13.1, 4.1 Hz, 1H), 0.96 (s, 3H), 0.91 (s, 3H), 0.89 (s, 9H), 0.04–0.00 (m, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3) δ 217.6, 142.7, 141.9, 121.5, 112.2, 82.8, 67.2, 58.3, 46.5, 46.4, 41.7, 40.4, 36.2, 36.1, 35.4, 34.4, 29.8, 28.8, 26.7, 26.0, 24.1, 21.6, 21.2, 18.2, 16.1, –4.7, –4.7. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{29}\text{H}_{46}\text{O}_4\text{SiNa}$ 509.3058; found 509.3058.

9.2. Synthesis of Substrate 22a

21 (300 mg, 0.616 mmol) was dissolved in anhydrous THF (5 mL) and MeOH (5 mL) in a flame-dried round-bottom flask. The reaction vessel was flushed with N_2 for 15 min while being cooled to -20°C in an ice/salt mixture. NaBH_4 (28 mg, 0.74 mmol, 1.5 equiv) was added, and the reaction was left to stir for 2 h at -20°C . After the first 1 h, another equivalent of NaBH_4 was added to the reaction. After stirring for another 4 h, checking that all starting material was consumed by TLC, $\text{NH}_4\text{Cl}_{(\text{sat.})}$ (10 mL) was added to quench the reaction. The aqueous phase was extracted with EtOAc (15 mL $\times$ 3) and DCM (10 mL $\times$ 4). The organic layer was then washed with brine (40 mL), dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to provide a 9.6:1 mixture of the desired diastereomer **22a** and its α 16-epimer. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc = 19:1 to 9:1) to afford **22a** (207 mg, 0.423 mmol) in a 69% yield as a white solid along with the minor diastereomer **α 16-22a** (21.6 mg, 44 μmol , 7.1%). Unreacted starting material **21** was recovered as well (4 mg, 70% brsm). R_f : 0.5 in 4:1 hexanes/EtOAc. Mp 200°C . $[\alpha]_D^{27} +9.5$ (c = 0.07, CHCl_3). IR (film, cm^{-1}): 2926, 2855, 2360. ^1H NMR (700 MHz, CDCl_3) δ 7.40 (d, J = 1.8 Hz, 1H), 7.31 (s, 1H), 6.42 (s, 1H), 4.37 (s, 1H), 4.06 (d, J = 3.5 Hz, 1H), 3.04 (d, J = 6.9 Hz, 1H), 2.67 (s, 1H), 2.34 (dd, J = 14.5, 6.0 Hz, 1H), 2.28 (s, 1H), 1.91 (d, J = 14.5 Hz, 1H), 1.86 (dt, J = 13.2, 3.4 Hz, 2H), 1.84–1.77 (m, 2H), 1.63–1.58 (m, 1H), 1.58–1.54 (m, 2H), 1.53–1.44 (m, 2H), 1.39 (td, J = 12.9, 9.5 Hz, 3H), 1.30–1.14 (m, 6H), 0.92 (s, 3H), 0.88 (s, 9H), 0.82 (s, 3H), 0.02 (s, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3) δ 142.7, 141.6, 121.5, 113.9, 86.0, 73.8, 67.4, 55.0, 48.5, 42.1, 41.6, 40.9, 36.2, 35.8, 35.5, 34.4, 29.9, 29.9, 28.9, 27.0, 26.0, 24.0, 22.1, 21.5, 18.3, 17.2, –4.7, –4.7. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{29}\text{H}_{48}\text{O}_4\text{SiNa}$ 511.3214; found 511.3220.

9.3. Synthesis of substrate 22

22a from above (145 mg, 0.297 mmol) was dissolved in anhydrous DCM (4.5 mL) and then transferred to an oven-dried round-bottom flask. The reaction vessel was flushed with N_2 for 15 mins. Then, DMAP (3.6 mg, 29 μmol , 0.10 equiv) and Ac_2O (283 μL , 2.98 mmol) were added at room temperature. Then, anhydrous pyridine (1.5 mL) was added to the reaction solution and left to stir for 16 h at room temperature. After checking that all starting material was consumed by TLC, MeOH (1 mL) and $\text{NH}_4\text{Cl}_{(\text{sat.})}$ (10 mL) were added in succession to quench the reaction. The aqueous phase was extracted with EtOAc (20 mL $\times$ 4). The organic layer was then washed with brine (25 mL), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes/

EtOAc = 19:1 to 9:1) to afford **22** (134 mg, 0.252 mmol) in an 85% yield as a white solid. R_f : 0.54 in 4:1 hexanes/EtOAc. Mp 143–145 °C. $[\alpha]_D^{27} -5.5$ ($c = 0.2$, CHCl_3). IR (film, cm^{-1}): 2976, 2849, 2890, 2855, 1732. ^1H NMR (700 MHz, CDCl_3): δ 7.28 (s, 1H), 7.19 (s, 1H), 6.51 (s, 1H), 5.53 (td, $J = 8.7, 1.7$ Hz, 1H), 4.05 (s, 1H), 3.23 (d, $J = 8.5$ Hz, 1H), 2.61 (dd, $J = 15.5, 8.9$ Hz, 1H), 1.89–1.82 (m, 2H), 1.81 (s, 3H), 1.59–1.50 (m, 4H), 1.47 (dd, $J = 14.5, 11.9$ Hz, 1H), 1.43–1.36 (m, 3H), 1.30 (td, $J = 13.8, 3.5$ Hz, 1H), 1.27–1.15 (m, 4H), 0.92 (s, 3H), 0.88 (s, 9H), 0.76 (s, 3H), 0.02 (s, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3): δ 170.4, 142.1, 141.6, 121.8, 114.5, 84.7, 74.2, 67.3, 53.0, 49.1, 42.1, 40.4, 40.3, 36.2, 35.9, 35.4, 34.4, 29.9, 28.9, 26.9, 26.0, 24.0, 21.5, 21.3, 21.2, 18.3, 16.8, –4.7, –4.7. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{31}\text{H}_{50}\text{O}_5\text{SiNa}$ 553.3320; found 553.3350.

10. Synthesis of Oleandrigenin (7) from 22

10.1. Synthesis of 7a

22 (63 mg, 0.12 mmol) was dissolved in anhydrous DCM (6.0 mL) and then transferred to a flame-dried 20 mL borosilicate glass test tube, which contained rose bengal (6.0 mg, 6.1 μmol , 0.05 equiv) under an atmosphere of N_2 with a rubber septum cap. Then, DIPEA (250 μL , 1.4 mmol, 12 equiv) was added to the reaction solution. The reaction vessel was then cooled to –78 °C for 15 min. The reaction was then irradiated with a 500 W wall-mounted flood lamp, at a stationary distance of approximately 10 cm for efficient radiation. The nitrogen line was then replaced with a balloon filled with oxygen, and the reaction was stirred while being irradiated for 6 h. After the confirmation of no more starting material by TLC, the light source was removed, as well as the oxygen balloon. The reaction was then allowed to stir while warming to room temperature while being flushed with an argon balloon to remove any remaining oxygen. The test tube was then covered with aluminum foil and left to stir for 16 h. Then, the solvent was removed *via* a nitrogen stream and redissolved in MeOH (6 mL) and cooled in an ice bath to 0 °C. Then, NaBH_4 (314 mg, 8.3 mmol, 70 equiv) was added over 1 h to reduce excessive bubbling. The reaction was then stirred at 0 °C for 1 h and then at room temperature for 1 h. After the listed time, the reaction was then chilled to 0 °C and diluted with EtOAc (15 mL). Then, a solution of 20% $\text{H}_2\text{SO}_4/\text{MeOH}$ was added dropwise until the pink/red color was dissolved away to leave an off-yellow solution. The reaction solution was then poured into DI water (20 mL). The aqueous phase was extracted with EtOAc (15 mL $\times$ 3). The organic layer was then washed with $\text{NaHCO}_3(\text{sat.})$ (30 mL), brine (30 mL), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc = 9:1 to 1:1 and then hexanes/acetone 9:1 to 3:2) to afford **7a** (33.2 mg, 60 μmol , 51%) as a viscous clear oil and oleandrigenin (**7**) as a white film (5.2 mg, 12 μmol , 10%). R_f : 0.64 1:1 hexanes: EtOAc. $[\alpha]_D^{27} -3.03$ ($c = 1.28$, CHCl_3). IR (film, cm^{-1}) 2976, 2849, 2890, 2855, 1732. ^1H NMR (600 MHz, CDCl_3) δ 5.96 (t, $J = 1.9$ Hz, 1H), 5.47 (td, $J = 9.3, 2.6$ Hz, 1H), 4.99 (dd, $J = 18.2, 1.9$ Hz, 1H), 4.85 (dd, $J = 18.1, 1.8$ Hz, 1H), 4.04 (t, $J = 2.8$ Hz, 1H), 3.18 (d, $J = 8.7$ Hz, 1H), 2.72 (dd, $J = 15.6, 9.7$ Hz, 1H), 1.96 (s, 3H), 1.85 (ddd, $J = 13.6, 9.4, 4.3$ Hz, 1H), 1.82–1.79 (m, 1H), 1.78–1.72 (m, 2H), 1.71–1.65 (m, 1H), 1.59–1.49 (m, 5H), 1.43 (ddd, $J = 15.5, 8.3, 2.9$ Hz, 2H), 1.40–1.36 (m, 2H), 1.30 (td, $J = 13.5, 3.5$ Hz, 1H), 1.25–1.20 (m, 3H), 1.16 (dd, $J = 14.8, 11.0$ Hz, 1H), 0.92 (s, 3H), 0.91 (s, 3H), 0.87 (s, 9H), 0.01 (d, $J = 1.8$ Hz, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3) δ 174.2,

170.5, 168.0, 121.5, 84.4, 75.8, 74.1, 67.2, 56.3, 50.1, 42.0, 41.3, 39.4, 36.0, 35.7, 35.3, 34.3, 29.8, 28.8, 26.7, 26.0, 23.9, 21.3, 21.2, 21.0, 18.2, 16.1, -4.7, -4.7. HRMS (ESI-TOF) m/z : $[M + Na]^+$ calcd for $C_{31}H_{50}O_6SiNa$ 569.3269; found 569.3251.

10.2. Synthesis of Oleandrigenin (7)

7a (18.4 mg, 33.7 μ mol) was dissolved in anhydrous THF (1.5 mL) and then transferred to a plastic screw-cap vial. To a second separate plastic screw-cap reaction vial was added HF·Py (70%, 456 μ L, 100 equiv) and then was diluted with anhydrous pyridine (456 μ L, *careful, exotherm!*). After the solution cooled to room temperature, the prepared HF·Py solution was added to the plastic vial containing the starting reagent. The reaction was left to stir for 18 h at room temperature. After the confirmation of no more starting material by TLC, TMSOMe (1.5 mL) was added to quench the reaction, followed by $NaHCO_3$ (sat.) (2 mL). After leaving to stir for 20 min, the reaction was extracted with EtOAc (3×15 mL). Then, the organic phase was dried with brine (20 mL), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc = 1:1 and then hexanes/acetone 4:1 to 3:2) to afford oleandrigenin (**7**) (13.2 mg, 30.5 μ mol, 91%) as a white solid. R_f 0.5 in 3:2 hexane/acetone. Mp: 220 °C (decomposition). $[\alpha]_D^{23}$ -3.25 (c = 0.56, $CHCl_3$). IR (film, cm^{-1}) 3511, 2931, 1788, 1745, 1692, 1258. 1H NMR (600 MHz, $CDCl_3$) δ 5.97 (t, J = 1.9 Hz, 1H), 5.48 (td, J = 9.3, 2.7 Hz, 1H), 4.98 (dd, J = 18.1, 1.9 Hz, 1H), 4.86 (dd, J = 18.1, 1.9 Hz, 1H), 4.14 (t, J = 2.9 Hz, 1H), 3.19 (d, J = 8.7 Hz, 1H), 2.74 (dd, J = 15.6, 9.7 Hz, 1H), 1.97 (s, 3H), 1.92–1.84 (m, 2H), 1.78 (dd, J = 15.6, 2.8 Hz, 2H), 1.74–1.67 (m, 1H), 1.55 (ddt, J = 16.5, 7.6, 3.4 Hz, 5H), 1.51–1.47 (m, 1H), 1.48–1.41 (m, 1H), 1.40–1.33 (m, 1H), 1.33–1.28 (m, 2H), 1.21 (ddd, J = 21.8, 11.7, 3.5 Hz, 1H), 0.95 (s, 3H), 0.94 (s, 3H). $^{13}C\{^1H\}$ NMR (151 Hz, $CDCl_3$) δ 174.1, 170.5, 167.8, 121.6, 84.4, 75.8, 74.0, 66.8, 56.3, 50.1, 41.9, 41.4, 39.4, 36.0, 35.6, 35.4, 33.4, 29.7, 28.0, 26.4, 23.8, 21.2, 21.1, 20.9, 16.1. HRMS (ESI-TOF) m/z : $[M + Na]^+$ calcd for $C_{25}H_{36}O_6Na$ 455.2404; found 455.2403.

11. Synthesis of Glycosyl Donor 28 (22,25)

11.1. Synthesis of 28a

l-Rhamnose monohydrate (2.00 g, 11.0 mmol) and acetic anhydride (5.0 equiv, 5.6 g, 54.9 mmol) were added to a flame-dried 50 mL round-bottom flask. The flask was flushed with nitrogen, and anhydrous pyridine (1.0 M, 11 mL) was added to the flask to give a clear solution. The solution was stirred until the starting material was consumed by TLC (8 h). The solution was concentrated *in vacuo*. The crude oil was dissolved in EtOAc (100 mL) and washed with 1 N HCl (20 mL), saturated aqueous $NaHCO_3$ (50 mL $\times$ 2), and then brine (50 mL). The organic layer was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The per-acetylated crude material was moved forward without further purification. The crude oil was dissolved in anhydrous CH_2Cl_2 (0.1 M, 110 mL) and then flushed with N_2 before adding PhSH (1.5 equiv, 1.7 mL, 16.5 mmol) and then $BF_3 \cdot Et_2O$ (3.0 equiv, 4.1 mL, 32.94 mmol). The solution gradually turned pink and was stirred overnight. The solution was quenched with excess saturated aqueous $NaHCO_3$ and stirred vigorously until the color disappeared (5–10 min). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (30 mL). The organic layers were concentrated *in vacuo*,

and the crude material was brought up in EtOAc (100 mL) and washed with saturated aqueous NaHCO₃ (50 mL) and then brine (50 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc = 5.7:1 to 3:1) to afford an inseparable 3:1 α/β diastereomeric mixture of known product **28a** (3.53 g, 9.22 mmol) in an 84% yield over two steps as a white solid. *R*_f 0.70 in 1:1 hexane/EtOAc. Mp 100–105 °C [α]_D²⁵ –68.4 (*c* = 0.59, CHCl₃). IR (thin film): 2977, 1743, 1583 cm⁻¹. Major diastereomer: ¹H NMR (500 MHz, CDCl₃): δ 7.49–7.44 (m, 2H), 7.35–7.27 (m, 3H) (overlapping), 5.50 (dd, *J* = 3.4, 1.6 Hz, 1H), 5.41 (d, *J* = 1.6 Hz, 1H), 5.29 (dd, *J* = 10.1, 3.3 Hz, 1H), 5.14 (t, *J* = 9.9 Hz, 1H), 5.11 (t, *J* = 9.8 Hz, 0H), 4.36 (dq, *J* = 9.7, 6.2 Hz, 1H), 2.21 (s, 1H), 2.14 (s, 3H), 2.08 (s, 3H), 2.01 (s, 3H), 1.25 (d, *J* = 6.2 Hz, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 170.2, 170.1, 170.1, 133.4, 132.0, 129.3, 128.0, 85.8, 71.5, 71.3, 69.5, 67.9, 21.1, 21.0, 20.8, 20.8, 17.5. Minor diastereomer: ¹H NMR (500 MHz, CDCl₃): δ 7.52–7.49 (m, 2H), 7.35–7.27 (m, 3H) (overlapping), 5.65 (dd, *J* = 3.7, 1.2 Hz, 1H), 5.11 (t, *J* = 9.8 Hz, 1H) (overlapping), 5.01 (dd, *J* = 10.1, 3.5 Hz, 1H), 4.90 (d, *J* = 1.4 Hz, 1H), 3.55 (dq, *J* = 9.7, 6.2 Hz, 1H), 2.21 (s, 3H), 2.05 (s, 3H), 1.98 (s, 3H), 1.32 (d, *J* = 6.1 Hz, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 170.4, 170.3, 170.0, 133.5, 132.2, 129.3, 128.2, 85.6, 75.1, 72.0, 71.2, 70.4, 20.9, 20.8, 17.9. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₈H₂₂O₇SNa 405.0984; found 405.0993.

11.2. Synthesis of 28b

Per-acetylated l-rhamnose thioglycoside **28a** (1.17 g, 4.58 mmol) was added to a flame-dried N₂-flushed 50 mL round-bottom flask. The flask was charged with anhydrous methanol (0.2 M, 24 mL) until a clear solution was formed. A piece of Na (catalytic quantity) was cut and washed with hexane to remove kerosene and then added to the solution. The solution was stirred until the starting material was consumed by TLC (30 min), which was indicated by a color change from clear to yellow. The reaction was quenched with glacial acetic acid and then K₂CO₃. The solution was concentrated *in vacuo*. The white solid was dissolved in acetone (50 mL) and passed through a silica plug. The organic layer was concentrated *in vacuo* to afford an inseparable 3:1 α/β diastereomeric mixture of known compound **28b** (1.17 g, 4.40 mmol) in a 96% yield as a white foam. *R*_f 0.58 in acetone. Mp 39.0–43.7 °C. [α]_D²⁵ –207 (*c* = 0.49, CHCl₃). IR (film, cm⁻¹) 3371, 2975, 2932, 2870, 1584. Major diastereomer: ¹H NMR (500 MHz, CD₃OD): δ 7.50–7.43 (m, 2H) (overlapping), 7.35–7.19 (m, 3H) (overlapping), 5.38 (d, *J* = 1.6 Hz, 1H), 4.10–4.00 (m, 2H) (overlapping), 3.65 (dd, *J* = 9.4, 3.3 Hz, 1H), 3.50–3.42 (m, 1H) (overlapping), 1.27 (d, *J* = 6.2 Hz, 3H). ¹³C NMR (126 MHz, CD₃OD): δ 136.0, 132.6, 130.1, 128.4, 90.2, 74.1, 73.9, 72.9, 71.0, 17.8. Minor diastereomer: ¹H NMR (500 MHz, CD₃OD): δ 7.50–7.43 (m, 2H) (overlapping), 7.35–7.19 (m, 3H) (overlapping), 4.95 (s, 1H), 4.10–4.00 (m, 2H) (overlapping), 3.50–3.42 (m, 1H) (overlapping), 3.38 (t, *J* = 9.2 Hz, 1H), 1.33 (d, *J* = 6.1 Hz, 3H). ¹³C{¹H} NMR (126 MHz, CD₃OD) δ 137.2, 131.1, 129.9, 127.8, 88.5, 77.9, 75.9, 74.2, 73.6, 18.2. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₂H₁₆O₄SNa 279.0662; found 279.0665.

11.3. Synthesis of 28c

Using a modification of the previously reported method, (25)**28b** was converted to **28c** as follows. l-Rhamnose thioglycoside **28b** (1.20 g, 4.71 mmol) and (1*S*)-(–)-10-camphorsulfonic acid (10 mol %, 122 mg, 0.52 mmol) were dissolved in anhydrous acetone

in a flame-dried, N₂-flushed 50 mL round-bottom flask. 2,2-Dimethoxypropane (10 equiv, 8.0 mL, 65.2 mmol) was then added to the reaction and stirred until all the starting material was consumed by TLC (45 min). The yellow reaction was diluted with CH₂Cl₂ (150 mL) and then washed with saturated aqueous NaHCO₃ and water. The clear organic layer was then dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was pushed forward without further purification. The flask containing the crude material was flushed with N₂ and then charged with CH₂Cl₂ (0.1 M, 47 mL). The flask was then charged with imidazole (1.5 equiv, 481 mg, 7.07 mmol) and then tert-butyldimethylsilyl chloride (1.2 eq, 852 mg, 5.66 mmol). The solution was warmed to 35 °C and stirred overnight under a N₂ atmosphere. The reaction was concentrated *in vacuo*, then brought up in EtOAc (100 mL), and washed with water and brine. The organic layer was then dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc = 5.7:1) to afford an inseparable 3:1 α/β diastereomeric mixture of known **28c** (1.80 g, 4.57 mmol) in a 97% yield over two steps as a clear oil. *R*_f 0.68 in 9:1 hexane/EtOAc [α]_D²⁵ -111.2 (*c* = 0.64, CHCl₃). IR (film, cm⁻¹) 2955, 2930, 2895, 2856. Major diastereomer: ¹H NMR (500 MHz, CDCl₃): δ 7.44–7.34 (m, 2H) (overlapping), 7.23–7.13 (m, 3H) (overlapping), 5.63 (s, 1H), 4.23 (d, *J* = 5.6 Hz, 1H), 3.97–3.84 (m, 2H), 3.31 (dd, *J* = 9.6, 7.1 Hz, 1H), 3.19 (dq, *J* = 8.9, 6.2 Hz, 1H), 1.42 (s, 3H), 1.25 (s, 3H), 1.08 (d, *J* = 6.2 Hz, 3H), 0.85–0.76 (m, 9H) (overlapping), 0.05 (s, 3H), -0.01 (s, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 133.9, 131.9, 129.1, 128.5, 127.6, 109.3, 84.1, 79.0, 76.4, 67.8, 28.3, 26.7, 26.0, 25.8, 18.3, 17.8, -3.8, -4.7. Minor diastereomer: ¹H NMR (500 MHz, CDCl₃) δ 7.44–7.34 (m, 2H) (overlapping), 7.23–7.13 (m, 3H) (overlapping), 4.94 (d, *J* = 2.1 Hz, 1H), 4.30 (dd, *J* = 5.6, 2.2 Hz, 1H), 3.43–3.36 (m, 1H), 1.49 (s, 3H), 1.30 (s, 3H), 1.22 (d, *J* = 6.2 Hz, 3H), 0.85–0.76 (m, 9H) (overlapping), 0.05 (s, 3H), 0.00 (s, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 135.6, 130.7, 129.1, 129.1, 127.3, 110.4, 84.1, 80.7, 76.6, 76.2, 75.4, 28.2, 26.6, 26.0, 18.6, 18.2, -3.4, -3.9. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₂₁H₃₄O₄SiNa 433.1839; found 433.1834.

11.4. Synthesis of **28d**

Protected thioglycoside **28c** (1.46 g, 3.56 mmol) and K₂CO₃ (5.0 equiv, 2.50 g, 17.8 mmol) were dissolved in a 15:1 acetone/H₂O (0.1 M, 36 mL). To the vigorously stirred solution, *N*-bromosuccinimide (1.5 equiv, 949 mg, 5.33 mmol) was added in a single portion. The reaction was monitored by TLC until full consumption of starting material (30–60 min) and was quenched with saturated aqueous NaHCO₃ (30 mL). The mixture was concentrated *in vacuo* until all acetone was removed and then extracted with EtOAc (30 mL × 3). The pooled organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc = 5.7:1) to afford an inseparable 2:1 α/β diastereomeric mixture of known compound **28d** (959 mg, 3.04 mmol) in an 86% yield as a white solid. *R*_f 0.3 in 4:1 hexane/EtOAc. Mp 79–82 °C [α]_D²⁵ -2.8 (*c* = 0.15, CHCl₃). IR (film, cm⁻¹) 3429, 2986, 2955, 2931, 2903, 2857. Major diastereomer: ¹H NMR (500 MHz, CDCl₃): δ 5.31 (s, 1H), 4.16 (d, *J* = 6.0 Hz, 1H), 4.09 (td, *J* = 6.1, 2.7 Hz, 1H) (overlapping), 3.92–3.83 (m, 1H), 3.50–3.38 (m, 1H) (overlapping), 2.91 (d, *J* = 4.6 Hz, 1H), 1.52 (s, 3H), 1.35 (s, 3H), 1.25 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.15 (s, 3H), 0.09 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 109.3, 92.5, 78.3, 76.1, 75.0, 67.4, 28.0, 26.3, 26.0, 18.4, 18.2, -4.0, -4.8. Minor diastereomer: ¹H NMR

(500 MHz, CDCl₃): δ 4.98 (d, J = 9.8 Hz, 1H), 4.21 (dd, J = 6.1, 2.3 Hz, 1H), 4.09 (td, J = 6.1, 2.7 Hz, 1H) (overlapping), 3.55 (d, J = 11.6 Hz, 1H), 3.50–3.38 (m, 1H) (overlapping), 1.53 (s, 3H), 1.37 (s, 3H), 1.29 (d, J = 6.0 Hz, 3H), 0.88 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 110.3, 92.4, 80.0, 75.0, 74.4, 73.3, 27.7, 26.5, 25.9, 18.8, 18.1, –4.1, –4.7. HRMS (ESI-TOF) m/z : [M + Na]⁺ calcd for C₁₅H₃₀O₅SiNa 341.1760; found 341.1748.

11.5. Synthesis of 28

28d (969 mg, 3.04 mmol) and trichloroacetonitrile (12.0 equiv, 3.66 mL, 36.5 mmol) were dissolved in anhydrous CH₂Cl₂ (0.1 M, 30 mL) in a flame-dried, N₂-flushed 100 mL round-bottom flask. To the vigorously stirred solution, 1,8-diazabicyclo[5.4.0]undec-7-ene (0.30 equiv, 136 μ L, 0.91 mmol) was added in a single portion. The reaction was monitored by TLC until full consumption of starting material (30 min), as indicated by a gradual color change from clear to dark red. The reaction was concentrated *in vacuo* and immediately purified by flash column chromatography on silica gel (hexanes/Et₃N = 49:1) to afford **28** (1.28 g, 2.77 mmol) as a single diastereomer in a 91% yield as a white solid. R_f : 0.51 in 9:1 hexane/EtOAc. Mp 98–101 °C. [α]_D²⁵ –28.7 (c = 0.54, CHCl₃). IR (film, cm^{–1}): 3348, 2986, 2955, 2934, 2902, 2857, 1671. ¹H NMR (500 MHz, C₆D₆) δ 8.53 (s, 1H), 6.85 (s, 1H), 4.29 (d, J = 5.8 Hz, 1H), 4.15 (dd, J = 7.2, 5.8 Hz, 1H), 4.03 (dq, J = 9.9, 6.3 Hz, 1H), 3.57 (dd, J = 9.7, 7.2 Hz, 1H), 1.43 (s, 3H), 1.33 (d, J = 6.2 Hz, 3H), 1.15 (s, 3H), 0.99 (s, 8H), 0.28 (s, 3H), 0.12 (s, 3H). ¹³C{¹H} NMR (126 MHz, C₆D₆) δ 160.4, 109.6, 96.2, 91.3, 79.3, 76.3, 75.5, 69.5, 28.2, 26.3, 26.2, 18.4, 18.0, –3.7, –4.7. HRMS (ESI-TOF) m/z : [M-CONHCCl₃]⁺ calcd for C₁₅H₂₉O₄Si⁺ 301.1830; found 301.1823.

12. Glycosylation of Oleandrigenin (7) Leading to Rhodexin B (2)

12.1. Synthesis of Intermediate 29

7 (13.2 mg, 0.030 mmol) was added to an oven-dried 1 dram vial and transferred to a glovebox, where Pd(ACN)₄(BF₄)₂ (1.4 mg, 0.003 mmol, 0.1 equiv) was added. Then, the vial was removed from the glovebox and flame-dried 4 Å M.S. (30 mg) was added to the reaction vial and then flushed with N₂ for 15 min. Subsequently, the reaction mixture was dissolved in DCM and chilled to –78 °C. **7** was dissolved in anhydrous DCM (1.3 g/10 mL = 0.28 M) in a separate flame-dried 1 dram vial and 1 equiv of donor **28**²¹ was added to the reaction vial, and an additional 0.5 eq of **28** was added every 45 min until 3.0 equiv was added in total. The resulting mixture was stirred for an additional 1 h at –78 °C. Subsequently, the reaction was diluted with benzene (1 mL) and filtered through celite, concentrated *in vacuo*, and then purified by silica gel chromatography (5% EA/hexanes to 20% EA/hexanes) to yield **29** (17 mg, 0.023 mmol, 76%) as a clear semisolid oil. R_f : 0.59, 20% EA/hexanes. [α]_D²⁵ –8.9 (c = 0.35, CH₂Cl₂). IR (film, cm^{–1}): 3494, 2928, 2856, 1777, 1620, 1245, 1079. ¹H NMR (700 MHz, CDCl₃) δ 5.97 (d, J = 1.9 Hz, 1H), 5.48 (td, J = 9.2, 2.6 Hz, 1H), 5.02 (s, 1H), 4.98 (dd, J = 18.1, 1.9 Hz, 1H), 4.85 (dd, J = 18.0, 1.8 Hz, 1H), 4.08 (d, J = 5.7 Hz, 1H), 4.00 (t, J = 6.4 Hz, 1H), 3.97 (d, J = 3.2 Hz, 1H), 3.60 (dq, J = 9.7, 6.3 Hz, 1H), 3.32 (dd, J = 9.7, 7.1 Hz, 1H), 3.19 (d, J = 8.7 Hz, 1H), 2.73 (dd, J = 15.7, 9.6 Hz, 1H), 1.97 (s, 3H), 1.86 (ddt, J = 13.9, 9.6, 4.3 Hz, 1H), 1.77 (dd, J = 15.8, 2.6 Hz, 1H), 1.71 (dd, J = 13.1, 3.0 Hz, 2H), 1.68–1.66 (m, 2H), 1.60–1.53 (m, 4H), 1.52 (s, 3H),

1.50–1.47 (m, 1H), 1.44 (dd, J = 14.1, 3.7 Hz, 2H), 1.38 (s, 1H), 1.36 (s, 3H), 1.31 (dd, J = 13.0, 3.8 Hz, 1H), 1.27–1.24 (s, 8H), 1.19 (d, J = 6.2 Hz, 4H), 0.94 (s, 3H), 0.93 (s, 3H), 0.90 (s, 9H), 0.15 (s, 3H), 0.09 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3) δ 174.0, 170.4, 167.6, 121.4, 108.8, 94.8, 84.3, 79.2, 76.1, 75.6, 73.9, 70.9, 65.9, 56.1, 49.9, 41.8, 41.2, 39.2, 36.3, 35.6, 35.1, 30.3, 29.7, 29.1, 28.2, 26.5, 26.4, 26.4, 25.9, 23.7, 21.0, 21.0, 20.8, 18.1, 17.7, 15.9, –4.0, –4.8. HRMS(ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{40}\text{H}_{65}\text{O}_{10}\text{Si}$ 733.4342; found 733.4339.

12.2. Synthesis of Rhodexin B (2)

29 (7.0 mg, 9.5 μmol) was dissolved in methanol (0.5 mL), and 1 N HCl in MeOH (100 μL) was added to the reaction vial dropwise. The reaction mixture was stirred at room temperature for 2 h. Then, solid NaHCO_3 was added until pH = 7, filtered through celite, adsorbed on silica, and purified by column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ = 1:0 to 10:1 to 5:1) to afford rhodexin B (**2**) in a 87% yield (4.8 mg, 8.3 μmol) as a white film, R_f = 0.45 (10% MeOH in CH_2Cl_2). Mp 238–240 °C (decomposition), reported mp: 242–244 °C. $[\alpha]_{\text{D}}^{25}$ –12 (c = 0.22, MeOH). IR (film, cm^{-1}): 3406, 2926, 1731, 1713, 1245, 1071, 1049. ^1H NMR (500 MHz, methanol- d_4) δ 6.00 (s, 1H), 5.50 (td, J = 9.2, 2.4 Hz, 1H), 5.04 (dd, J = 18.5, 1.9 Hz, 1H), 4.97 (dd, J = 18.5, 1.8 Hz, 1H), 4.79 (d, J = 1.8 Hz, 1H), 3.98 (t, J = 2.8 Hz, 1H), 3.78 (dd, J = 3.4, 1.7 Hz, 1H), 3.70 (td, J = 9.8, 3.3 Hz, 2H), 3.66 (d, J = 2.9 Hz, 1H), 3.39 (t, J = 9.5 Hz, 1H), 3.29 (d, J = 8.7 Hz, 1H), 2.81 (dd, J = 15.6, 9.6 Hz, 1H), 1.96 (s, 3H), 1.93 (d, J = 4.9 Hz, 1H), 1.89 (d, J = 2.5 Hz, 1H), 1.85 (m, 1H), 1.81 (m, 1H), 1.73 (dd, J = 12.0, 3.0 Hz, 1H), 1.68 (dd, J = 13.6, 3.5 Hz, 2H), 1.63 (dd, J = 11.6, 3.3 Hz, 1H), 1.60–1.54 (m, 2H), 1.51–1.48 (br, s, 1H), 1.47 (br, s, 1H), 1.44 (br, s, 1H), 1.29 (m, 4H), 1.27 (s, 2H), 1.25 (s, 2H), 1.23–1.19 (m, 1H), 1.21 (m, 1H), 0.98 (s, 3H), 0.96 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, $\text{CD}_3\text{OD}-d_4$) δ 176.7, 172.1, 171.6, 121.7, 99.9, 85.0, 77.6, 76.0, 74.1, 73.6, 73.0, 72.5, 70.0, 57.4, 51.4, 42.7, 41.4, 40.0, 38.1, 36.7, 36.3, 31.6, 30.8, 27.8, 27.5, 24.3, 22.2, 22.0, 20.9, 18.0, 16.4. HRMS(ESI) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{31}\text{H}_{46}\text{O}_{10}\text{Na}$; 601.2983, found 601.2976.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
 Natural β -C16-oxygenated cardenolides and summary of the synthetic studies towards oleandrigenin (7).

Scheme 1. Synthesis of key intermediate 9 from testosterone.

a) LDA, THF, -78°C then TMSCl; b) $\text{Pd}(\text{OAc})_2$, MeCN, r.t., 65% yield, 2 steps; c) SiO_2 , DIPEA, toluene, 60°C ; 69% yield (95% BRSM).

Scheme 2. Installation of the C17 heterocycle and diastereoselective β 16-epoxidation

^a(a) Co(acac)₂ (17 mol %), PhSiH₃, O₂, 1,4-dioxane, rt; (b) N₂H₄·H₂O, Et₃N, EtOH, 50 °C, and then I₂, Et₃N, THF, rt 38% yield from **9**; (c) furan-3-ylboronic acid (**13**), Pd(PPh₃)₂Cl₂ (10 mol %), NaHCO₃, PhMe/MeOH/H₂O, 80 °C, 76% yield; (d) *m*CPBA, NaHCO₃, DCM, −40 to −20 °C, 77% yield, >20:1 dr; (e) **14**, Pd(PPh₃)₄, CuCl, LiCl, DMSO, 60 °C, 42% (80% BRSM); and (f) *t*-BuO₂H, VO(acac)₂ (5 mol %), CH₂Cl₂, 0 °C, 1.5 h, 70% yield, >20:1 dr.

Scheme 3.

Studies on epoxide isomerization leading to the installation of the β -16 configuration.

Scheme 4. Synthesis of oleandrigenin (7)

^a(a) BF₃·OEt₂ (10 mol %), dioxane, rt, 1 min, 95% yield; (b) NaBH₄, MeOH/THF (1:1), -20 °C, 76% yield, 9.6:1 dr; (c) Ac₂O, DMAP, Py, rt, 85% yield; (d) (1) Rose Bengal, DIPEA, DCM, -78 °C, 16 h, rt; (2) NaBH₄, MeOH, 0 °C to rt; (3) 20% H₂SO₄/MeOH, rt, 51% yield (+10% of **7**); and (e) HF·Pyr, THF, rt, 91% yield.

Scheme 5.
Studies toward the synthesis of rhodexin B

Scheme 6.
Studies toward the synthesis of rhodexin B

Table 1.Model studies focused on the optimization of the ¹⁴-hydration conditions

entry	catalyst	loading(mol%)	oxidant	solvent	11 : 12 ^a	conversion(%) ^a
1	$\text{Co}(\text{acac})_2$	17	O_2	1,4-dioxane	1.5 : 1	99
2	$\text{Mn}(\text{dpm})_3/\text{pph}_3$	17	O_2	EtOH	1 : 1	99
3	$\text{Fe}(\text{acac})_3$	2.5	$p\text{-O}_2\text{NC}_6\text{H}_4\text{SO}_2\text{Cl}$	MeOH	10 : 1	99

^aEstablished by ¹H NMR analysis of the crude reaction mixtures.