Discoveries and Challenges en Route to Swinhoeisterol A

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Abstract: In this work, a full account of the authors’ synthetic studies is reported that culminated in the first synthesis of 13(14→8),14(8→7)diabeo-steroid swinhoeisterol A as well as the related dankasterones A and B, 13(14→8)abeo-steroids, and periconiastone A, a 13(14→8)abeo-4,14-cyclo-steroid. Experiments are described in detail that provided further insight into the mechanism of the switchable radical framework reconstruction approach. By discussing failed strategies and tactics towards swinhoeisterol A, the successful route that also allowed an access to structurally closely related analogues, such as Δ23-24-epi-swinhoeisterol A, is eventually presented.

Introduction

Traditionally, the majority of bioactive compounds has been isolated from terrestrial plants and fungi, whereas the marine biosphere was more difficult to access. Undersea organisms often produce structurally highly complex, rearranged secondary metabolites with unique bioactivities.[1]

An increasing number of chemical syntheses relies on biogenetic information, gaining access to natural products via biomimetic approaches.[2] Still, many of the proposed pathways are established without the support of co-isolated biosynthetic precursors from the producing organism. Commonly, biogenetic proposals anticipate polar pathways to account for skeletal rearrangements and radical routes are rarely considered.[3] One class of steroidal natural products with such rearranged skeletons are the so-called abeo-steroids, which display one or several C–C bond migrations with respect to the classic, tetracyclic steroid backbone.[4]

In recent years, our group as well as others have demonstrated that key synthetic transformations (possibly biomimetic in nature) can indeed be carried out using radical reactivity, giving the desired skeletal modifications with high selectivity as shown in the syntheses of rearranged steroids cortistatin A,[5] aplysiasecosterol A,[6] strophasterol A,[7] strophasterol A,[7d] pleurocian A/matsutakone,[8] and herbarulide.[9] It was also a cascade of rearrangements initiated by an alkoxy radical that cleared the way to the dankasterone[13(14→8)abeo-steroids][10] and the swinhoeisterol class of natural products [13(14→8),14(8→7)diabeo-steroids].[11] Only recently, we achieved the synthesis of swinhoeisterol A (2), its 24-epi-counterpart (24-epi-2), dankasterone A (3) and B (4), and periconiastone A (5).[12] The 4,14-cyclo aldo product of the latter, starting from commercial ergosterol (1) by exploiting a radical cascade (Scheme 1).[13] Regarding the biological activities of these natural products, dankasterone A (3) and B (4) show significant cytotoxicity against the P388 lymphocytic leukemia test system (ED50: 2.2 and 2.8 µg mL−1, respectively)[10] whereas diabeo-steroid swinhoeisterol A (2) exhibits a remarkable inhibition of the histone acetyltransferase (h)pa300 with an IC50 of 2.9 µM.[11a] The most recently isolated

Scheme 1. Structures of the abeo-steroids swinhoeisterol A (2), dankasterone A (3) and B (4), and periconiastone A (5), their common synthetic starting material, ergosterol (1), as well as their generic classes.

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secondary metabolite, periconiastone A (5), is reported to display intriguing antibacterial activity against two Gram-positive microbial pathogens, namely S. aureus (MIC 4 µg mL⁻¹) and E. faecalis (MIC 32 µg mL⁻¹).[12]

Herein, we want to report on the evolution of our synthetic studies towards swinhoesterol A (2) and its 24-epi-isomer (24-epi-2) as well as present experimental support for our mechanistic proposal for our radical framework reconstruction approach.

Results and Discussion

Our rationale to gain synthetic access to the rearranged skeletons of abeo-steroids relied on the initial generation of an alkoxy radical. The following radical rearrangement (Scheme 2) enabled the synthesis of the above-mentioned natural products and selective access to either the mono- or diaboe-skeleton was gained by adapting the reaction conditions (Phl(OAc)₃/I₂) for the former; HgO/I₂, for the latter) to generate B, starting from a γ-hydroxy enone A. Subsequent δ scission of the C13–C14 bond in B would form an intermediary 14-oxo functionality along with a stabilized tertiary radical at C13 (C). An attack onto the Aδ-bond generates α-keto radical D, which is either quenched reductively to give the 13(14-8)abeo skeleton (E) as present in the dankasterones class of natural products, or further reacts in a Dow–Beckwith rearrangement.[15]

This comprises of an attack of the C7-centered radical to the 14-oxo functionality to give alkoxy radical F. Another β scission, this time of C8-C14, yields the 13(14-8),14(8-7)diaboe core (G) of the swinhoesters after abstraction of an H atom (G → H).

Initially, 5α-hydroxy enone 7 was chosen as a substrate for the envisioned radical rearrangement (Scheme 3). As we described in our synthesis of herbarulide,[9] the preparation of Burawoy’s ketone (6) following reported procedures has proven to lack reproducibility.[16] Aiming for a stepwise oxidatio

of ergosterol (1), 6 was available in 62% yield over 4 steps.[9] Reduction with zinc in acetic acid provided 5 in an acceptable yield of 59%. To generate 7, diaboe skeletons were drawn at 50% probability. Reagents and conditions: a) Zn (29 equiv.), HOAc, 90 °C, 3 h, 47%; b) SeO₂ (4.75 equiv.), BuOH/pyridine (4:1), 80 °C, 4 h, 59%; c) Pb(OAc)₃ (2.0 equiv.), I₂ (2.0 equiv.), CaCO₃ (2.0 equiv.), CH₃CN, 85 °C, 2 h, 8: 18%, 9: 59%, 10: traces. CCDC 1991055 (9) and 1991054 (10) contain the supplementary crystallographic data (see Experimental Section).

Scheme 2. Mechanistic proposal for the alkoxy radical initiated framework reconstruction leading to the structural precursors of the dankasterones E and swinhoesters H.

Scheme 3. Radical rearrangement of 7 leading to the 13(14-8),14(8-7)diaboe structures 8, 9, and 10. ORTEP plots of 9 and 10. Thermal ellipsoids are drawn at 50% probability.

Philip Heretsch was born in Lippstadt, Germany, in 1982. He obtained his PhD degree from Universität Leipzig (supervisor: A. Gian-nis) in 2009. After a postdoctoral stay with K.C. Nicolaou at The Scripps Research Institute, La Jolla, California, and at Rice University, Houston, Texas, he was appointed assistant professor at Freie Universität Berlin in 2015. Philipp Heretsch has been working in the total synthesis of natural products since the beginning of his career. His group is now pursuing framework reconstruction strategies for the synthesis of abeo-steroids and alkaloids, guided by biosynthetic hypotheses.
Pb(OAc)$_4$, 59% of 9, only traces of 10, and 18% of 15β-iodo diene 8 were obtained.

To prevent formation of the oxygen adduct and to keep options for later A-ring functionalization, elimination of the tertiary alcohol in Burawoy’s ketone (6) was carried out using thionyl chloride and basic conditions to give Δ⁴-enone 11 (75% yield). In this case, standard Riley conditions gave Δ⁴-hydroxy enone 12 as another substrate for the radical cascade. Again, the Pb(OAc)$_4$/I$_2$-system was used leading to a different product distribution for “open flask” and “degassed” conditions (see Scheme 4). Tetraene diene 13 was isolated as the major product (31% yield) and its yield could be improved to 44% when carefully degassing the reaction mixture. Under “open flask” conditions, 4-iodo substituted endoperoxides 16 and 17 were obtained in 12 and 23% yield, respectively, or in 9 and 11% for the “degassed” experiment. The formation of 16 and 17 presumably results from remaining traces of oxygen in the reaction mixture. Interestingly, aerobic conditions led to the isolation of 15β-iodo tetraene diene 14 (14%) whereas oxygen-free conditions delivered the 13(14—8)abeo species 15 (13%), instead, providing first confirmation of our mechanistic proposal (Scheme 2).

Gaining synthetic access to the swinhoeisterols by further processing one or several of the obtained products was tested on tetraene diene 13 (Scheme 5) as well as epimeric 4-iodo endoperoxides 16 and 17 (Scheme 6). For 13, we envisioned to reduce the oxo-functionality at C6 to the corresponding allylic alcohol, which could then be used to perform a sigmatropic rearrangement, either directly (Johnson–Claisen), after acetylation (Ireland–Claisen), or after methyl stannylation ([2,3]-Wittig–Still), thereby installing a precursor for the exo-methylene function at C4. However, no conversion of starting material was observed when applying Johnson–Claisen conditions to the allylic alcohol and in case of the [2,3]-Wittig–Still rearrangement, addition of nBuLi to the methyl stannylated alcohol only resulted in the formation of the 1,2-rearranged product. In case of the Ireland–Claisen reaction, the allylic acetate was successfully converted to the corresponding silyl ketene acetal as judged by ¹H NMR, but further reaction to the desired carboxylic acid was not successful.

Scheme 4. Radical rearrangement of 12 and product distributions depending on the reaction conditions. Reagents and conditions: a) SOCl$_2$ (4.5 equiv.), pyridine, –10°C, 45 min, 75%; b) SeO$_2$ (4.75 equiv.), dioxane/H$_2$O (50:1), 65°C, 5 h, 73%; c) Pb(OAc)$_4$ (2.0 equiv.), I$_2$, CaCO$_3$, 85°C, 2 h, R as in Scheme 3.

Scheme 5. Attempted sigmatropic rearrangements to introduce a synthetic precursor for the desired exo-methylene unit.

Scheme 6. Synthetic transformations of endoperoxides 16 and 17 and mechanistic proposal for the rearrangement to 20. Reagents and conditions: a) PtO$_2$ (0.2 equiv.), H$_2$ (balloon), EtOAc, 25°C, 4 h; b) Ag$_2$O, THF, 25°C, 1 h, 56% (2 steps); c) PtO$_2$ (0.2 equiv.), H$_2$ (balloon), EtOAc, 25°C, 4 h, 70%; d) Ag$_2$O, THF, 60°C, 16 h, 85%, R as in Scheme 3.
Since the diastereomeric endoperoxides 16 and 17 contained the structural motif of a $\Delta^1$-9α-hydroxy ketone, which is also present in other members of the swinholisteroids, they were also assumed valuable intermediates en route to 2 (Scheme 6). Thus, reduction of the peroxide functionality to the corresponding 5,9-diol (as in 19) was carried out on both 4-ido epimers using $\text{PtO}_2/H_2$. In case of 4β-iodo endoperoxide 16, a mixture of the diol (not shown) and epoxide 18 resulting from concomitant $S_n2$ reaction was obtained. Full conversion was possible by treatment with $\text{Ag}_2\text{O}$ and gave 18 in 56% over 2 steps. As 18 was deemed a suitable precursor for further transformations (e.g., Wharton transposition), diol 19 was to be transformed to 18 as well through a $S_n1$ reaction. Treatment with $\text{Ag}_2\text{O}$ showed no conversion at room temperature but after 16 h at 60 °C selective formation of a new product was observed. Careful analysis of the NMR data obtained led us to propose the structure of lactone 20, which was confirmed by X-ray single crystal structure analysis. Presumably, formation of the expected cation at C4 did indeed take place but was immediately or concertedly followed by bond migration to give 10(S)-4abeo intermediate I.

Assumedly, this oxocarbenium facilitated an attack of the C9 hydroxyl and thereby set the stage for a benzilic acid-type rearrangement ring contraction/expansion\[8\] (see structure J) yielding lactone 20, which features immense connectivity changes in the A and B ring. To the best of our knowledge, this structural motif has not been observed in any steroidal context, before. Afore mentioned Wharton transposition was envisioned to convert epoxide 18 to C4 allylic alcohol, but as the initial conversion to the corresponding hydrazone was unsuccessful, further studies employing iodo-endoperoxides 16 and 17 were discarded.

Another compound isolated from the reaction of Pb(OAc)$_2$/I$_2$ was $\Delta^5$-13(14-8)abeo-sterol 15. Although not further employed in the synthesis of the swinholisteroids, its isolation supported our mechanistic proposal and transformation to dankasterone A (3) in 56% yield over two steps (Scheme 7) was successful. In the meantime, we were able to provide proof of the cage-like 13(14-8)abeo-4,14-cyclo structure of periconiastone A (5)\[15\] by X-ray single crystal analysis. Previously, we had synthesized 5 from dankasterone B (4)\[15\] and now set out to explore the possibility to generate an enolate by 1,4-reduction of dankasterone A (3), which would then undergo aldol addition and give the desired 4,14-cyclo skeleton. Interestingly, reaction with L-selectride only gave 3α-αlcohol 21, the product of 1,2-reduction, presumably due to steric inaccessibility of C5.

As so far, all our efforts to process any rearranged material obtained towards swoinholisterol, and for a further generalization of the radical cascade, next γ-hydroxy enone 22 which was accessible in 4 steps and 42% from ergosterol (1)\[7\] was to be investigated. When treating 22 with Pb(OAc)$_2$/I$_2$, four main products were obtained after careful separation (Scheme 8A). Once more, two of those contained the diabeo-structure (triene dione 25 and its 15β-ido analogue 26); the other two being 13(14-8)abeo dione 23 and its 7α-ido analogue 24. To further substantiate our mechanistic proposal, 23 as well as 24 were both separately treated with Pb(OAc)$_2$/I$_2$. As expected, no conversion of the starting material was observed in case of
dione 23, but the reaction of iodide 24 gave rise to 63% of diabeo-compound 25. As we reported earlier, it was possible to selectively access either the diabeo-framework (25, HgO/I₂, 68% yield) or the monoadeo-skeleton (24, Phil(OAc)₃, 76% yield), depending on the conditions to generate the initial alkoxyl radical.²⁰ To test if the rearrangement to the diabeo-structures could be initiated without employing toxic Hg or Pb reagents, 22 was treated with Ag₂O and I₂.²⁰ However, only elimination of the 14-hydroxyl was observed (to give 27) along with partial i-steroidal opening to give iodide 27 as a mixture of epimers (5%S/5%R),²¹ Knowles’ photocatalytic ring expansion conditions²² either did not yield any rearranged product but resulted in the isolation of Δ⁶,1⁴-steroid 29.²¹ Any other attempts to initiate a radicals-promoted cascade employing other metal salts, did not lead to any conversion of the starting material.

To further study the influence of the stereoconfiguration at C14 on the radical cascade, we prepared 14β-hydroxy enone 34 (Scheme 9). Since all Riley oxidations carried out resulted in 14α-hydroxylation, a Schenck ene reaction followed by reduction of the hydroperoxide was envisioned, instead. i-Steroid enone 30 was converted into TMS dienol ether 31, which was then treated with oxygen and TPP as photosensitizer under irradiation with white light to give 14α-hydroperoxide 32 and 14β-hydroperoxide 33 (56 and 12% yield, respectively). While 14α-OOH 32 could be converted to 13(14)-diabeo-dione 23 in a yield of 38% using Daniell’s conditions (FeSO₄) ⟷ (14α)-OOH 33 was reduced to the corresponding alcohol 34, which was then exposed to Pb(OAc)₄/I₂. This time, no rearrangement of the steroid skeleton was observed. The alkoxyl radical generated at C14 rather added to the double bond at C8, giving rise to an epoxide and the C7 centered radical was then quenched by iodine leading to 7α,13-epoxide 35. This difference in reactivity can be explained with an unfavorable orbital overlap of the radical SOMO and the π-orbital of the C13–C14 bond so that no β scission could occur.

As the radical rearrangement was most selective on the i-steroid system, it was chosen as starting material for our synthetic efforts towards swinhoeisterol A (2) and analogues. In the following, we want to discuss the major synthetic challenges that had to be overcome en route to swinhoeisterol A (Scheme 10). Starting from ergosterol (1), our synthetic approach consisted of an oxidative cleavage/olefination/hydrogenation sequence of Δ²³ to introduce the desired (saturated) campestan side chain (Scheme 10, A). We envisioned to introduce the exo-methylene moiety via elimination of a hydroxy-methyl group at C4 at a late stage of the synthesis making use of an enone functionality in the A-ring (Scheme 10, B). This key intermediate was traced back to a diene dione system from our radical cascade (Scheme 10, C).

Following these studies, we attempted a synthetic approach towards swinhoeisterol A (2) making use of 25 (Scheme 11), which was obtained in a good yield from 22 when applying HgO/I₂ (68%). It was possible to differentiate the C6- and C14-oxo functionalities of diene dione 25 by selective formation of 14 sily enol ether 36. We planned to adjust the oxidation state by 1,6-reduction with Selectride, which along with the expected reduction involved the incorporation of an oxygen at C9 to give 9α-hydroxy dione 37 presumably through attack of O₂ by the intermediary dienolate. Even though this was not the expected product, the synthetic route was continued, since the obtained 9α-hydroxy enone pattern is present in swinhoeisterol B (not shown). Reduction with LiAlH₄ gave de-silylated 6α-OH 38, which seemed to be a suitable precursor for
an i-steroid opening. However, when treating 38 with acetic acid and BF$_2$OET$_2$, an unexpected anthrasteroid 39 was isolated in 87%. Presumably, the initial i-steroid opening took place as expected (K) but was followed by generation of cation L through loss of the hydroxy group. Stabilization of the cation by bond migration could then lead to spiro-compound M, which, after formation of the C1–C6 bond, gives Weland complex N. Loss of a proton would generate aromatic 39, whose 1(10)abeo-structure can be found in a number of natural products.

Through these experiments, the tertiary alcohol at C9 had been identified to be problematic in the cyclopropane opening reaction of 38 and, thus, its formation was tried to be avoided by vigorous exclusion of oxygen prior to reduction with L-selectride (Scheme 12). The so-generated Δ3-ene dione system tautomeralized (Scheme 10, C), leading to a tedious isolation accompanied by decomposition. To prevent this problem, we decided to add another reducing reagent to the reaction mixture to convert one or both ketones to the corresponding alcohols. Interestingly, the initially formed lithium enolate protected the respective ketone against reduction with lithium aluminum hydride, and only the 6-oxo moiety was reduced to give β-hydroxy ketone 40. Its treatment with BF$_2$OET$_2$ and acetic acid again resulted in an undesired side reaction, i.e., isomerization of Δ3 into conjugation with the ketone to give Δ5,5-diene 41 as the major product (51%) and only minor quantities (12%) of the desired Δ5,3-diene 42. Saponification (K$_2$CO$_3$, MeOH) proved to be difficult on 42, and de-acetylation could only be achieved under reductive conditions (DIBAI-H) leading to concomitant reduction of the 14-oxo functionality to furnish 43. To instead employ Δ5,5-diene 41, several approaches were investigated, but isomerization of one or both of the two double bonds proved to be impossible. We suspected that isomerization of Δ3 had occurred due to activation of the ketone with BF$_2$OET$_2$, and, thus, reduced 40 to 6,14-diol 44. Fortunately, this time no isomerization was observed during i-steroid opening and subsequent de-acetylation (DIBAI-H) gave 3,14-diol 45 in a convincing yield of 74% over 2 steps. Employing Oppenauer conditions to achieve oxidation and isomerization to enone 45 did not lead to any conversion. Hence, a stepwise process using Dess–Martin periodinane and then DBU established key-intermediate 45 with a yield of 79% over 2 steps.

As a handle to construct the requisite exo-methylene group along with the necessary trans ring junction of the A and B ring (Scheme 10, B), we envisioned the installation of a hydroxymethyl group at C4 and elimination of the primary alcohol to furnish the methylene unit. Initially, we intended to install the remaining carbon atom through a reductive alklylation protocol under dissolving metal conditions. As the direct addition of gaseous formaldehyde did not yield any of the desired hydroxy methylated product, the trapping as a silyl enol ether was investigated. We applied a procedure described by Mueller and Gillick [25] which involved the generation of so-called lithium bronze. Thus, enone 45 was readily converted into silyl enol ether 46 (Scheme 13). To introduce a suitable methylene precursor, a variety of conditions to alkylate 46 were tested. Methods using aqueous formaldehyde either in
combination with Lewis acids such as Sc(OTf)$_3$[27] or Yb(OTf)$_3$[28] or by addition of a de-silylating reagent (e.g., TBAF[29]) have been described. Even though addition of formaldehyde could be detected by mass spectrometry, the isolation of the desired γ-hydroxy ketone was unsuccessful and instead, ketone 47 was obtained, the product of a retro-aldol reaction.[30] To circumvent this problem, we attempted to install a protected hydroyxymethyl moiety. However, when treating silyl enol ether 46 with BOMCl and varying Lewis acids,[31] only α-halogenated ketones were isolated, yielding 4-chloro- and 4-fluoro-ketones when using SnCl$_4$, TiCl$_4$, or BF$_3$·OEt$_2$, respectively. Consequently, the introduction of other functional groups known to be convertible into a methylene group was considered. Thus, treatment of silyl enol ether 46 with ethyl bromo acetate to give the corresponding ethyl ester[32] or Eschenmoser’s salt to give the dimethylamine,[33] were attempted but did not yield any desired product other than ketone 47.

Alternatively, the method by Nishiyama and Stork[33] was considered and successfully executed to introduce the C4 hydroxymethyl moiety. Thus, enone 45 was selectively reduced under Luche conditions to the corresponding allylic alcohol, which was then treated with chloro(bromomethyl)dimethylsilane and triethyl amine to give the crucial precursor for a radical cyclization. Initial results employing the (bromomethyl)siyl ether (not shown) in the radical cyclization and subsequent Tamao oxidation[34] lacked reproducibility. An alternative procedure employing stoichoimetric amounts of the tin reagent required the corresponding (iodomethyl)siyl ether 48.[35] Hence, allylic alcohol was converted to the (chloromethyl)siyl ether (not shown) followed by Finkelstein reaction to give iodide 48. Radical cyclization was then achieved by treatment with catalytic quantities of AIBN and nBu$_2$SnCl and stoichio- metric amounts of NaBH$_4$ to result in the formation of a oxasilolane (not shown), which, upon oxidative work up (H$_2$O$_2$, KF), delivered diol 49 in 36% yield along with 16% of its undesired β-epimer. Finally, the primary alcohol was converted to the corresponding triflate with Tf$_2$O at ~78°C, which, upon warming to 25°C, eliminated to yield the desired exo-methyl group in Δ$^{24}$-epi-swinhoeisterol A Δ$^{24}$-epi-2.[27]

With a reliable route for swinhoeisterol A’s tetracyclic core, one last synthetic challenge had to be overcome, i.e., the introduction of the correctly configurated side chain (Scheme 10, A). It was deemed strategically advantageous, to perform the necessary modifications at a late stage. Since we envisioned a sequence of oxidative C-C bond cleavage, olefination, and hydrogenation, many synthetic intermediates bearing easily accessible double bonds additional to Δ$^{24}$ had to be excluded a priori. Thus, hydroxymethylated 49 and enone 45 presented themselves as promising candidates (Scheme 14). Oxidative Δ$^{24}$ bond cleavage on the stage of diol 49 was achieved through ozonolysis and reductive workup. Attempted Julia–Kocienski olefination proved unsuccessful due to low solubility of the starting material. Thus, the 1,3-diol functionality of 49 was protected as an acetonide, which was processed to the corresponding aldehyde. Again, no conversion of the starting material in an attempted Julia–Kocienski reaction could be observed. We, thus, shifted our attempts towards enone 45. Ozo- nolysis gave aldehyde 50, and this time, Julia–Kocienski olefi- nation using sulfone 51 indeed led to conversion of starting material. Unfortunately, not the desired olefin, but tetrazole 52, which presumably arose from aldol reaction between enolizable C7 and the 22-oxo functionality followed by trapping of the alcohohite by the tetrazole moiety of sulfone 51, was isolated. As a consequence of this reactivity, i-steroid diol 44, an intermediate without the oxo moiety at C14, was anticipated to adopt a less reactive conformation and, thus, seemed to be a better choice. However, treatment of the corresponding alde- hyde of diol 44 with LiHMDS and sulfone 51 only led to isola- tion of material with the C6 hydroxyl bearing a tetrazole sub- stituent. One of the few remaining intermediates to conduct the ozonolysis/olefination approach was β-hydroxy ketone 40, which, after conversion to aldehyde 53 eventually afforded the desired olefin 55 (with the double bond being Z configurated) along with small quantities of aldol product 54. Fortunately, it was possible to almost suppress formation of 54 (less than 5%) when increasing the amount of sulfone 51 (5.0 equiv.).
That way, olefin 55 was obtained in 86% yield. To furnish the desired saturated campestane side chain, hydrogenation conditions were tested on olefin 55, but no conversion of starting material was observed under the conditions employed. Further reduction experiments were then carried out on diol 56, which was obtained by reduction with NaBH₄.

Hydrogenation of a 22Z double bond is known to be more difficult than the corresponding 22E isomer. In agreement, in most experiments no conversion was achieved (Table 1, entries 3–9) and only elevated hydrogen pressure (40–60 bar) led to complete conversion to 57. Unfortunately, varying degrees of epimerization at C24 occurred during the course of this reaction yielding up to 50% of the undesired ergostane product when using Pd/C (entry 1) and still 25% when Pt/C was used (entry 2). Attempted alternatives, such as Wilkinson's (entry 6) or Crabtree's catalyst (entry 7) as well as Shenvi's radical hydrogenation method (entries 8 and 9) did not lead to any conversion of starting material.

As hydrogenation of a 22E-configurated double bond without epimerization of C24 was deemed more promising, we carried out several isomerization experiments to convert 22Z to 22E, but could eventually not succeed in identifying a viable method. At this point, we turned our attention to rather functionalize the side chain double bond and remove the thus-installed functional group reductively in a separate step. Introduction of sulfur-containing functionalities failed and halogenation with bromine to the dibromide and subsequent treatment with AlBN/nBu₃SnH only led to a mixture of 22E- and 22Z-diol 56. To our delight, hydroboration and subsequent oxidation with NaOH/H₂O₂ afforded primarily a 6,14,23-triol (not shown) under concomitant reduction of C14. Acetonide formation of the thus-obtained 1,3-diol unit and functionalization of the side chain alcohol (predominantly 23-OH) to epoxide, followed by Barton-McCombie deoxygenation eventually gave the desired saturated campestane side chain without any epimerization (Scheme 15).

All synthetic challenges were thus coped with so that rather similar approaches led to the synthesis of natural swinhoeisterol A (2, b-series) and 24-epi-swinhoeisterol A (24-epi-2, a-series). As it was initially uncertain at which stage an installation of the correct side chain fragment would be feasible, the synthetic route had also been carried out in the ergostane series, starting from ergosterol (1) without hydrogenation of the Δ22 bond. This route enabled access to Δ22-24-epi-swinhoeisterol A (Δ22-24-epi-2) in 16 steps and a total yield of 1.5%.

In summary, access to the diabeso-skeleton (25 and 25a) via γ-hydroxy enones 22 or 22a was accomplished in five to six steps, respectively, starting from ergosterol (1). β-Hydroxy ketones 40 and 40a, obtained after reduction, were further processed following two different pathways. For the synthesis of swinhoeisterol A (2), 40a was subjected to ozonolysis and Julia–Kocienski olefination to give 55b, followed by a hydroboration, oxidation/Barton–McCombie deoxygenation sequence to yield the desired saturated campestane side chain as in 58b. Opening of the i-steroid moiety led to acetate 59b. 40 and 40a, on the other hand, were reduced to diols 44 and 44a and subsequent treatment with BF₃·OEt₂ under acidic conditions gave the corresponding acetates 59 and 59a. De-acetylation was accomplished using DIBAL-H giving rise to 43, 43a, and 43b. Oxidation with DMP and subsequent isomerization
Scheme 15. Overview of the synthetic routes to swinhoeisterol A (2, b series). 24-epi-swinhoeisterol A (24-epi-2, a series) and \( \Delta^{22} \)-24-epi-swinhoeisterol A (\( \Delta^{22} \)-24-epi-2) starting from ergosterol (1). Reactions and conditions: a) PtO (0.1 equiv.), H\(_2\) (20 bar), ETOAc, 25 °C, 24 h, 22a: 88%; b) HgO (2.7 equiv.), I\(_2\) (2.4 equiv.), C\(_6\)H\(_5\), 105 °C, 2 h, 25a: 68%; c) l-selectride (2.0 equiv.), THF, −78 °C, 1 h; then LIAH\(_7\) (2.0 equiv.), −78 to 0 °C, 1 h, 40: 55% 40a: 54%; d) O\(_2\), then PPh\(_3\), 60 °C, 2 h; e) LiHMDS (3.1 equiv.), THF, then (2.4 equiv.), H= 43b; f) BF\(_3\)-OEt\(_2\), HOAc then DBU, 73–79%, 2 steps; g) KF (10 equiv.), KHCO\(_3\) (2.0 equiv.), −78 to 25 °C, 1 h; then H\(_2\)O\(_2\) (1:1:2), 0 to 25 °C, 5 h, 59b: 82%; h) DIBAI-H, then 78%, 2 steps; i) NaBH\(_4\), Ce\(_3\)O\(_7\); j) CeCl\(_3\), pyridine (99:1), −78 °C, 24 h, 78%; k) DBU (0.2 equiv.), CH\(_2\)Cl\(_2\), 78 to 25 °C: 78% (2 steps); l) BF\(_3\)-OEt\(_2\), HOAc, 78–86%; m) NaBH\(_4\), Ce\(_3\)O\(_7\); n) NaBH\(_4\), Ce\(_3\)O\(_7\); o) Cl\(_2\), SiMe\(_3\), Et\(_2\)N, 71–83%, 2 steps; p) NaBH\(_4\), Ce\(_3\)O\(_7\); q) NaBH\(_4\), Ce\(_3\)O\(_7\); r) NaBH\(_4\), Ce\(_3\)O\(_7\); s) NaBH\(_4\), Ce\(_3\)O\(_7\); t) NaBH\(_4\), Ce\(_3\)O\(_7\); u) NaBH\(_4\), Ce\(_3\)O\(_7\); v) NaBH\(_4\), Ce\(_3\)O\(_7\); w) NaBH\(_4\), Ce\(_3\)O\(_7\); x) NaBH\(_4\), Ce\(_3\)O\(_7\); y) NaBH\(_4\), Ce\(_3\)O\(_7\); z) NaBH\(_4\), Ce\(_3\)O\(_7\).
of the Δ5 bond with DBU yielded enones 45, 45a, and 45b. Luche reduction and silylation with (chloromethyl)- or (bromomethyl)chlorodimethylsilane gave (chloromethyl)silyl ethers 60 and 60b, and (bromomethyl)silyl ether 61a, respectively. As classic Nishioka-Stork conditions (61a, AlBN, nBuSnH) followed by Tamao oxidation gave crucial diol 49a only in low and varying yields (15–34%), we adjusted the synthetic route towards Δ24-24-epi-2 and 2. (Chloromethyl)silyl ethers 60 and 60b were transformed to the corresponding (iodomethyl)silyl ethers using Finkelstein conditions and then treated with catalytic amounts of AlBN and nBuSnClI to give a stoichiometric amount of NaNH2CN prior to oxidation, facilitating a reliable access to diols 49 and 49b. Finally, triﬂation of the primary alcohol and subsequent elimination afforded 2, 24-epi-2, and Δ24-24-epi-2, respectively, bearing the characteristic exo-methylene group of the swinhoesterols.

Conclusion

We herein detailed our efforts towards the synthesis of swinhoesterol A (2) and discussed major challenges that were overcome during the development of a viable synthetic route. Additionally, the synthesis of the first analogue, Δ24-24-epi-swinhoesterol A (Δ24-24-epi-2) was outlined as well as several experiments that were carried out to support our mechanistic proposal for the radical framework reconstruction. Two unexpected rearrangements of the steroid skeleton were observed, one of them leading to hydroxy lactone 20, which had not been reported before. The synthesis of the remaining members of the swinhoesterol class and the biological evaluation of all synthesized natural products are ongoing in our laboratory.

Experimental Section

Crystallographic data: Deposition numbers 1999884 (5), 1991055 (9), and 1991054 (10) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: biomimetic synthesis · natural product synthesis · radical reactions · rearrangement · steroids

[1] A. L. J. Beckwith, D. M. O'Shea, S. Gerba, S. W. Westwood, P. T. W. Cheng, R. R. Knowles, J. Org. Chem. 2019, 84, 1045–1055.
[2] A. L. J. Beckwith, D. M. O'Shea, S. Gerba, S. W. Westwood, P. T. W. Cheng, R. R. Knowles, J. Org. Chem. 2019, 84, 1045–1055.
[3] A. L. J. Beckwith, D. M. O'Shea, S. Gerba, S. W. Westwood, P. T. W. Cheng, R. R. Knowles, J. Org. Chem. 2019, 84, 1045–1055.
[4] A. L. J. Beckwith, D. M. O'Shea, S. Gerba, S. W. Westwood, P. T. W. Cheng, R. R. Knowles, J. Org. Chem. 2019, 84, 1045–1055.
[5] A. L. J. Beckwith, D. M. O'Shea, S. Gerba, S. W. Westwood, P. T. W. Cheng, R. R. Knowles, J. Org. Chem. 2019, 84, 1045–1055.
[6] A. L. J. Beckwith, D. M. O'Shea, S. Gerba, S. W. Westwood, P. T. W. Cheng, R. R. Knowles, J. Org. Chem. 2019, 84, 1045–1055.
[7] A. L. J. Beckwith, D. M. O'Shea, S. Gerba, S. W. Westwood, P. T. W. Cheng, R. R. Knowles, J. Org. Chem. 2019, 84, 1045–1055.
[8] A. L. J. Beckwith, D. M. O'Shea, S. Gerba, S. W. Westwood, P. T. W. Cheng, R. R. Knowles, J. Org. Chem. 2019, 84, 1045–1055.
[9] A. L. J. Beckwith, D. M. O'Shea, S. Gerba, S. W. Westwood, P. T. W. Cheng, R. R. Knowles, J. Org. Chem. 2019, 84, 1045–1055.
[10] A. L. J. Beckwith, D. M. O'Shea, S. Gerba, S. W. Westwood, P. T. W. Cheng, R. R. Knowles, J. Org. Chem. 2019, 84, 1045–1055.
[11] A. L. J. Beckwith, D. M. O'Shea, S. Gerba, S. W. Westwood, P. T. W. Cheng, R. R. Knowles, J. Org. Chem. 2019, 84, 1045–1055.
[12] A. L. J. Beckwith, D. M. O'Shea, S. Gerba, S. W. Westwood, P. T. W. Cheng, R. R. Knowles, J. Org. Chem. 2019, 84, 1045–1055.
[13] A. L. J. Beckwith, D. M. O'Shea, S. Gerba, S. W. Westwood, P. T. W. Cheng, R. R. Knowles, J. Org. Chem. 2019, 84, 1045–1055.
[14] A. L. J. Beckwith, D. M. O'Shea, S. Gerba, S. W. Westwood, P. T. W. Cheng, R. R. Knowles, J. Org. Chem. 2019, 84, 1045–1055.
[15] A. L. J. Beckwith, D. M. O'Shea, S. Gerba, S. W. Westwood, P. T. W. Cheng, R. R. Knowles, J. Org. Chem. 2019, 84, 1045–1055.
[16] A. L. J. Beckwith, D. M. O'Shea, S. Gerba, S. W. Westwood, P. T. W. Cheng, R. R. Knowles, J. Org. Chem. 2019, 84, 1045–1055.
[17] A. L. J. Beckwith, D. M. O'Shea, S. Gerba, S. W. Westwood, P. T. W. Cheng, R. R. Knowles, J. Org. Chem. 2019, 84, 1045–1055.
[18] A. L. J. Beckwith, D. M. O'Shea, S. Gerba, S. W. Westwood, P. T. W. Cheng, R. R. Knowles, J. Org. Chem. 2019, 84, 1045–1055.
[19] A. L. J. Beckwith, D. M. O'Shea, S. Gerba, S. W. Westwood, P. T. W. Cheng, R. R. Knowles, J. Org. Chem. 2019, 84, 1045–1055.
[20] A. L. J. Beckwith, D. M. O'Shea, S. Gerba, S. W. Westwood, P. T. W. Cheng, R. R. Knowles, J. Org. Chem. 2019, 84, 1045–1055.
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