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Total Synthesis of Linckosides A and B, the Representative Starfish Polyhydroxysteroid Glycosides with Neuritogenic Activities

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Supporting Information

ABSTRACT: Linckosides A and B, two starfish metabolites with promising neuritogenic activities, are synthesized in a longest linear sequence of 32 steps and 0.5% overall yield; this represents the first synthesis of members of the polyhydroxysteroid glycoside family, which occur widely in starfishes.

Linckosides A (**1**) and B (**2**) were identified from an Okinawan starfish, namely, *Linckia laevigata* in 2002 during a screening for neuritogenic natural products, which could be candidates for the prevention and treatment of neurodegenerative diseases.[1a] The promising results led to further isolation and characterization of over 20 minor congeners, and the majority of these linckosides share a common cholesta-3β,6β,8β,15α,16β-pentahydroxy nucleus and a 2-*O*-methyl-β-D-xylopyranose residue at C3.[1] In fact, polyhydroxysteroid glycosides relevant to linckosides are common and characteristic metabolites in starfishes in which hydroxyl groups commonly occur at C6, C8, and C15 besides the biogenetic hydroxyl group at C3.[2] These metabolites of the slow-moving starfishes are believed to be the defense chemicals against parasites and predators, therefore are expected to possess a variety of pharmacological activities, such as antitumor and antibacterial activities. However, the poor accessibility of these molecules from natural sources has retarded in-depth studies on their activities. Chemical synthesis to attain these highly polar, fragile, and complex steroid glycosides poses also a formidable challenge;[3,4] to the best of our knowledge, none of the starfish polyhydroxysteroid glycosides has ever been synthesized to date.[4,5]

We envisioned the assembly of linckoside A/B from four pieces (Figure 1), including a polyhydroxysteroid C22 aldehyde (e.g., **3**), a side chain derivative (e.g., **4**), a 2-*O*-methyl-D-xylopyranosyl donor (e.g., **5**), and an L-arabinofuranosyl/D-xylopyranosyl donor (e.g., **6**/**7**). The polyhydroxysteroid aldehyde (**3**) could be elaborated from the easily accessible vespertilin acetate **8**[6] by exploiting the inherent functional groups at C3, C5/6, C16, and C22. Both the installation of the side chain onto the C22 aldehyde via a Julia olefination (**3** + **4**)[7] and the stereoselective glycosylation at C29-OH with donors (**6**/**7**) bearing a neighboring participating ester group under the mild gold(I)-catalyzed conditions[8] would be reliable tasks. A late-stage glycosylation at C3-OH with 2-*O*-methyl donor **5** was straightforward; however, the required β-selectivity would require scrutiny of the glycosylation conditions.[9] Given the dense functionality of the substrates, a successful sequence of transformations can only be determined by trial-and-error.

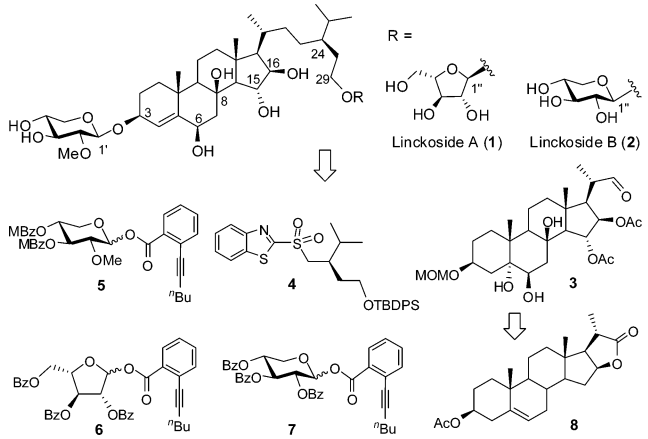

Figure 1. Linckosides A (**1**) and B (**2**) and a retrosynthetic plan.

The synthesis commenced with preparation of lactone **8** from the cheap industrial material diosgenin (4 steps, 53% yield; Supporting Information) (Scheme 1). Regioselective allylic bromination of **8** led to the corresponding C7-bromide as a mixture of epimers, which were in equilibrium in the presence of excess LiBr; subsequent treatment with *p*-toluenethiol and Et_3N provided β-sulfide **9** (79%).[10] The 3-*O*-acetyl group in **9** was replaced by a methoxymethyl group, which was found appropriate in the following transformations. The resulting **10** was then subjected to reduction (of the lactone); selective protection of the nascent 22-OH with a *tert*-butyldiphenylsilyl (TBDPS) group and oxidation of the 16-OH (with Dess-Martin periodinane) furnished C16-ketone **11** smoothly (85%). Treatment of **11** with a EtOAc solution of oxaziridine **12** resulted in an epimeric mixture of the corresponding sulfoxide, which underwent *cis*-elimination at 80 °C to yield the desired 5,7-diene **13** (80%).[10] Addition of oxaziridine **12** to a THF solution of ketone **13** and LiHMDS at −78 °C, a protocol developed by Davis et al.,[11] gave a satisfactory conversion, ensured by a relatively high concentration (ca. 0.3 M) of the lithium enolate and careful workup. Immediate reduction of the resultant acyloin with $NaBH(OAc)_3$ delivered the required 15α,16β-diol **14** in a decent 42% yield, without detection of the possible diastereoisomers.[12,13]

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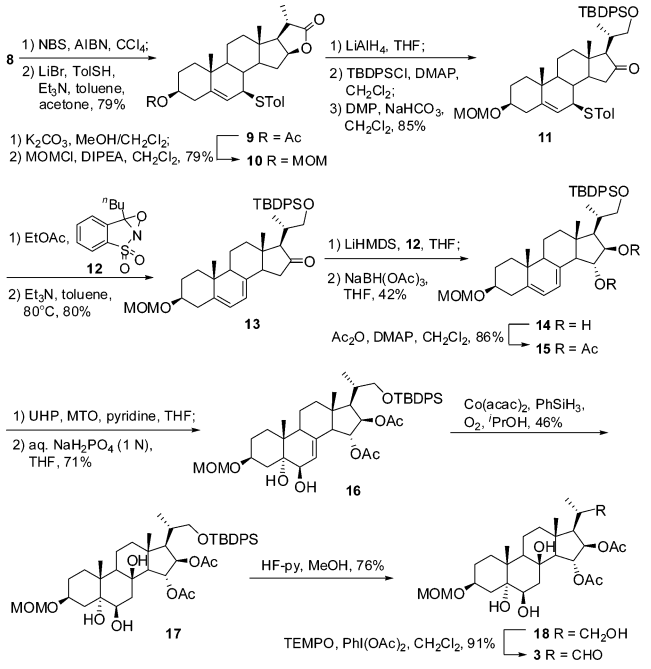
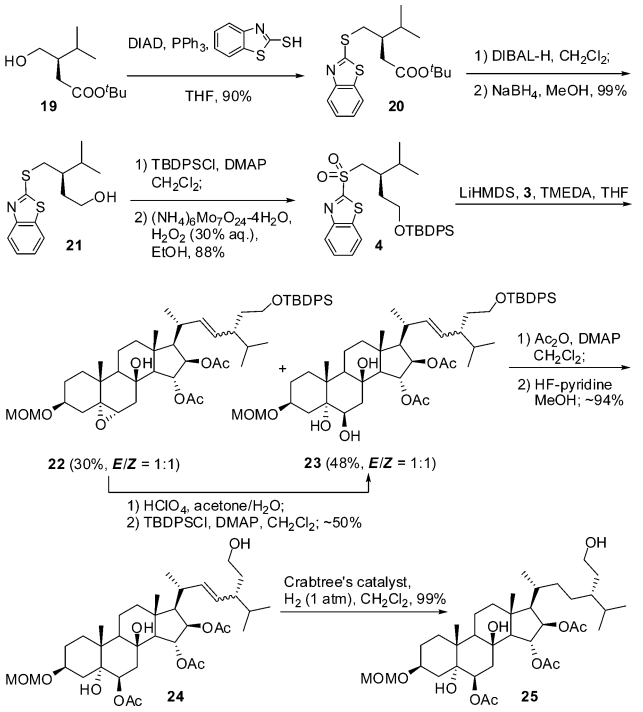
Scheme 1. Synthesis of Steroidal Aldehyde 3



Scheme 2. Synthesis of the Aglycon Derivative 25



The 15,16-OHs were masked with acetyl groups to give **15**. Selective epoxidation of the 5,6-ene in diene **15** was achieved with methyltrioxorhenium (VII) and urea hydrogen peroxide.[14] Successive hydrolysis with an aqueous NaH_2PO_4 solution in THF afforded 5α,6β-diol **16** in a good 71% yield.[15]

It was noted that few literatures have documented the installation of the steroidal C8-OH, which involved either dihydroxylation or epoxidation of 7,8-ene derivatives.[16] We failed at numerous attempts on substrates either before or after introduction of the 15,16/5,6 diols. Fortunately, application of the Mukaiyama hydration conditions[17] onto the advanced 7,8-ene **16** led to the desired 8β-ol **17** in appreciable yields. Under the optimized conditions (1.1 equiv of $Co(acac)_2$, 9.5 equiv of $PhSiH_3$, O_2, ^{i}PrOH, 50 °C), **17** was readily isolated in 46% yield. The downfield shift of the angular methyl H18 and H19 resonances in **17** compared to those in **16** (by 0.30 and 0.24 ppm, respectively) is consistent with a β configuration at C8.[16c,d] Removal of the silyl group provided tetraol **18**; selective oxidation of the resulting primary C22-OH was achieved with TEMPO and $PhI(OAc)_2$,[18] affording the desired aldehyde **3** in an excellent 91% yield. The structure of **3** was confirmed by an X-ray diffraction analysis (CCDC 1433646; Supporting Information).

Preparation of the side chain derivative **4** was straightforward (Scheme 2). Indeed, Mitsunobu substitution of the readily available chiral alcohol **19**[7d] with 2-mercaptobenzothiazole provided sulfide **20** (90%). The ester residue in **20** was reduced into alcohol by DIBAL-H and subsequently $NaBH_4$ (99%). Protection of the resulting hydroxyl group (in **21**) with a TBDPS group followed by oxidation of the sulfide with ammonium molybdate tetrahydrate and H_2O_2 afforded sulfone **4** smoothly (88%). The condensation of sulfone **4** and aldehyde **3** was realized under the modified Julia olefination conditions,[7] which necessitated LiHMDS (9.2 equiv) as a base and TMEDA (tetramethylethylenediamine, 18.4 equiv) as an additive. Nevertheless, besides the desired adducts **23** (48%, *E*/*Z* = 1:1), adducts **22** (30%, *E*/*Z* = 1:1) were obtained in that the 5α,6β-diol was converted into 5,6-α-epoxide via seemingly an S_N2 substitution of the sterically hindered 6β-OH by the antiperpendicular 5α-OH, which is much easier to be deprotonated. It was noticed that condensation with the corresponding 6-*O*-acetyl derivative led to the epoxide predominantly. All these products were separated; and the epoxide **22***E*/**22***Z* could be converted into 5α,6β-diol **23***E*/**23***Z* in ~50% yield (Supporting Information).[19] Surprisingly, the double bond in **23** was found to be inert toward hydrogenation under various conditions (Supporting Information), which might be attributable to its crowded surrounding. Therefore, after blocking the 6β-OH with an acetyl group (while the tertiary 5α,8β-OHs were inert toward acetylation), the bulky TBDPS group was removed to give **24**. Subjection of **24***E*/**24***Z* to hydrogenation in the presence of Crabtree's catalyst[20] afforded the saturated aglycon **25** quantitatively.

As expected, glycosylation of **25** at 29-OH with *o*-hexynylbenzoate donor **6** proceeded smoothly under the catalysis of PPh_3AuNTf_2 (0.2 equiv);[8] subsequent removal of the 3-*O*-MOM group with HCl in THF/H_2O facilitated the purification of the product to provide α-L-arabinofuranoside **26** in a good 72% yield (Scheme 3). Oxidation of the 3-OH (in triol **26**) with pyridinium chlorochromate in CH_2Cl_2 followed by treatment with HCl in dioxane led to the corresponding $\Delta^{4,5}$,3-one derivative,[21] which was subjected to Luche reduction to afford $\Delta^{4,5}$,3β-ol **27** (64%).[22] It was noted that direct dehydration of the 5α-OH in **17** after acetylation of 6β-OH was not successful.

The glycosylation of **27** with 3,4-di-*O*-*p*-methoxybenzoyl-2-*O*-methyl-D-xylopyranosyl *o*-hexynylbenzoate (**5**, α/β = 1:2.4) under the catalysis of PPh_3AuNTf_2 (0.2 equiv) in CH_2Cl_2 at −10 °C was proven to be optimal (see Supporting Information for model studies), affording the desired 3-*O*-β-glycoside **28** in an excellent 93% yield, with the α-anomer hardly detectable. Nevertheless, further studies are required to understand the mechanism behind this unusually high β-selectivity.[8d,9] Finally, all the acyl groups on **28** were cleaved cleanly with KOH in

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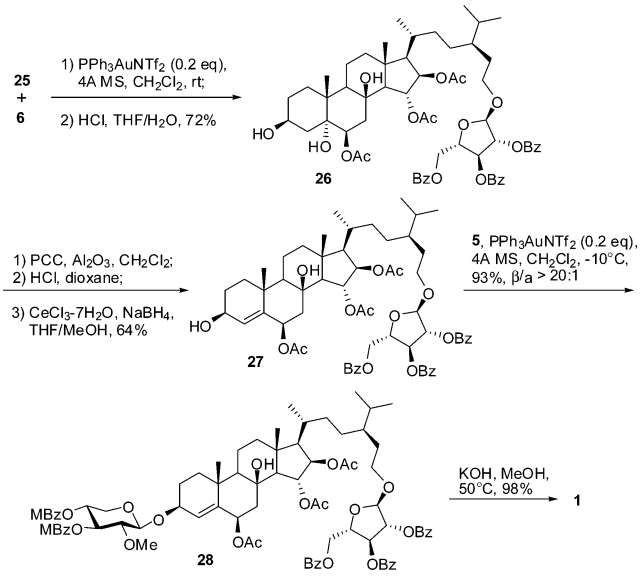
Scheme 3. Completion of the Synthesis of Linckoside A (1)



methanol at 50 °C, furnishing linckoside A (**1**) nearly quantitatively. By the same token, linckoside B (**2**) was synthesized starting from glycosylation of **25** with D-xylopyranosyl *o*-hexynylbenzoate **7** (Supporting Information). The analytic data of the synthetic **1** and **2** are identical to those reported for the natural products (Supporting Information).

Summarizing, the total synthesis of linckoside A/B (**1**/**2**) has been achieved from readily available materials in a modular sequence, which requires a longest 32 linear operations (in a total of 44 steps), and proceeded with 0.5% overall yield. The synthesis is easily adaptable to the synthesis of analogues and thus shall facilitate in-depth studies on the promising neuritogenic effects of linckosides. In addition, the present synthesis represents the first synthesis of members of the polyhydroxysteroid glycosides, which occur ubiquitously in starfishes and thus demonstrates the feasibility of synthetic access to this type of complex marine metabolites with a wide spectrum of biological activities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11276.

Synthetic procedures, characterization data, and NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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