Asymmetric Total Synthesis of Clionastatins A and B

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Supporting Information Placeholder

ABSTRACT: Herein we report the first total synthesis of polychlorinated steroids clionastatins A and B, which was accomplished asymmetrically by means of a convergent, radical fragment coupling approach. Key features of the synthesis include an Ireland–Claisen rearrangement to introduce the C5 stereocenter (which was ultimately transferred to the C10 quaternary stereocenter of the clionastatins via a traceless stereochemical relay), a regioselective acyl radical conjugate addition to join the two fragments, an intramolecular Heck reaction to install the C10 quaternary stereocenter, and a diastereoselective olefin dichlorination to establish the synthetically challenging pseudoequatorial dichlorides. This work also enabled us to determine that the true structures of clionastatins A and B are in fact C14 epimers of the originally proposed structures.

Chlorinated steroid drugs, such as the corticosteroids Temovate and Nasonex (Figure 1), are an important class of synthetic steroids with a variety of therapeutic uses. For example, Nasonex, the retail sales of which reached $376 million in 2018,¹ is prescribed as a treatment for nasal allergy symptoms and nasal polyps. Therefore, the development of efficient strategies to synthesize chlorinated steroids is highly desirable for exploration of their pharmaceutical applications. Interestingly, the chlorine atoms in most steroid natural products—for example, physalolactone,² blattellastanosides,³ and kihesterone D⁴—are found in chlorohydrin groups, which may originate from the corresponding epoxides. Two notable exceptions are the polychlorinated androstanes clionastatins A and B (1 and 2, Figure 1),⁵ which were isolated by Fattorusso et al. in 2004 from the burrowing sponge *Cliona nigricans*. The originally proposed structures (1a and 2a), including the relative stereochemistry, were established by NMR spectroscopy. However, no X-ray crystal structures were obtained and the ¹³C NMR spectra were also not registered, possibly because only approximately 1 mg of each compound was isolated. The complete ¹³C NMR assignment was deduced through inspection of the 2D NMR spectra HSQC and HMBC.⁶ Therefore, the accuracy of the reported ¹³C NMR data remains to be determined. Importantly, preliminary biological studies indicated that they exhibit potent cytotoxicity against tumor cell lines (IC₅₀ = 0.8–2.0 μg/mL).⁵

Scheme 1. Synthetic challenge and retrosynthetic analysis of clionastatins A and B.

A. Facile aromatization of the C19-hydroxyl dieneone compound

B. Retrosynthetic analysis of clionastatin A and B

Figure 1. Structures of representative chlorinated steroid drugs and polychlorinated steroids clionastatins A and B.
The clionastatins are the first polyhalogenated steroids to have been isolated from a natural source (either marine or terrestrial). Notably, the C1 and C2 vicinal dichlorides of these compounds are in the pseudoequatorial configurations, and thus are difficult to install synthetically because dihalogeneration of the C1–C2 olefin of steroid substrates tends to deliver diaxial products. Moreover, although the C19 chloride could conceivably be introduced through deoxychlorination of the corresponding C19 hydroxyl group,8,9 the B-ring dienone motif tends to aromatize in the presence of the C19 hydroxyl group, as evidenced by the easy formation of estrone 4 from dienone 3 even under mild conditions (Scheme 1A). On top of that, the clionastatins feature a unique 3,5,8(9)-16-tetraen-7,15-dione core, which distinguishes them from any other known steroid. The complicated polychlorination pattern and the highly unsaturated androstane framework, as well as the structural ambiguity make clionastatins a formidable synthetic challenge, and no completed synthesis of clionastatins has previously been reported.10 Herein we report the first total synthesis of clionastatins, which was accomplished asymmetrically via a convergent approach involving radical fragment coupling.11,12 Moreover, our synthetic studies resulted in revision of the originally proposed structures of these natural products.

As outlined in Scheme 1B, we anticipated that 2a could be accessed from 1a through regioselective chlorination at C16. We planned to introduce the C3–C5 diene of 1a at a late stage to avoid undesired aromatization of the B ring. Stereoselective olefin dichlorination has been a longstanding challenge in the synthesis of chlorinated natural products,17–24 and many elegant methods have been developed.25–31 We envisioned that olefin dichlorination directed by the C19 hydroxyl group of homoallylic alcohol 5 could be employed to introduce the chlorine atoms at C1 and C2 by means of a titanium-mediated selective dihalogenation method developed by Burns and co-workers.29,31 Furthermore, inspired by the pioneering work of Overman and colleagues,32,33 we envisaged that the cis-fused A/B-ring system of 5, including the C10 quaternary stereocenter, could be established by an intramolecular Heck reaction of enol triflate 6, which could in turn be assembled through a radical fragment coupling reaction between acyl telluride29–31 and known enone 8.36 Although there are three possible sites for acyl radical conjugate addition to 8, we anticipated that the desired C8 position would be the most reactive on the basis of steric and electronic factors. Acyl telluride 7 would be readily accessed from acid 9, which could be prepared from 10 by means of the Ireland–Claisen rearrangement.38 We expected to install the C1 stereogenic center of 10 via the Corey–Bakshi–Shibata reduction39 of known compound 11.40 Notably, the stereochemical information at C1 of 10 would be transferred to C5 of 9 by the Claisen–Ireland rearrangement, which would ultimately relay its stereochemical information to the C10 quaternary stereocenter of 5 by the intramolecular Heck reaction. Thus, the C10 quaternary stereocenter of the two clionastatins would be derived from C1 of 10 via a traceless stereocentric strategy.31,42

Scheme 2. Asymmetric total synthesis of clionastatins A and B.

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*Abbreviations: MOM, methoxymethyl; CBS, Corey-Bakshi-Shibata reagent; Ac, acetyl; KHMDS, potassium bis(trimethylsilyl)amide; TMS, trimethylsilyl; NMM, N-methylmorpholine; DIBAL-H, disobutylaluminum hydride; Tf, trifluoromethanesulfonyl; dppp, 1,3-bis(diphenylphosphino)propane; PMP, 1,2,2,6,6-pentamethylpiperidine; DMP, Dess-Martin periodinane; DMF, N,N-dimethylformamide; DMAP, N,N-4-dimethylaminopyridine; m-IBX, meta-iodoxybenzoic acid.*
Our synthesis commenced with the Corey–Bakshi–Shibata reduction of 11 (Scheme 2), which provided allylic acetate 10 in 93% yield with a 85% enantiomeric excess after in situ protection of the resulting hydroxyl group as an acetate. Ireland–Claisen rearrangement of 10 with potassium bis(trimethylsilyl)amide and trimethylisilyl chloride afforded carboxylic acid 9, which was then converted to acetyl telluride 7. Pleasingly, treatment of 7 with Et3B in air smoothly generated the corresponding acyl radical, which underwent conjugate addition to enone 8 exclusively at C8. Addition of MeOH to the reaction mixture was necessary to facilitate tautomerization of the resulting 1,3-diketone to the requisite C9 enol constitutional isomer (not shown), which was transformed to enol trflate 12 in 50% yield over two steps. Notably, the use of an acetyl telluride as the acyl radical precursor proved uniquely effective, other alternatives, such as an acyl selenide, failed to yield any conjugate addition products upon reaction with 8.

With 12 in hand, we turned our attention to the crucial intramolecular Heck reaction to install the C10 quaternary stereocenter. Unfortunately, the C7 and C15 carbonyl groups of 12 were found to be incompatible with various Heck cyclization conditions, which gave mainly enone 13 through elimination of the trifluoromethanesulfonyl group. To address this issue, we reduced 12 with NaBH₄ and CeCl₃ to give a mixture of diastereomeric 7,15-diol. Not shown, which underwent the desired intramolecular Heck reaction and subsequent in situ oxidation with Dess–Martin periodinane to afford 14 in 46% yield over two steps. Removal of the methoxymethyl protecting group of 14 delivered homoallylic alcohol 15, which set the stage for the pivotal diastereoselective olefin dichlorination to install the C1 and C2 pseudoequatorial dichlorides.

Our initial plan was to accomplish the olefin dichlorination through titanium-mediated selective dihalogenation of 15 by means of Burns’s protocol. However, dichlorination of 15 with C$_2$Ti(OiPr)$_2$ and BuOCl furnished desired dichloride 22 only as a minor product, along with undesired diastereomer 23 and oxetane 24 as major products (Scheme 3). Despite extensive experimentation (see Supporting Information for details), we were unable to minimize the formation of 23, and therefore searched for an alternative approach. We surmised that through careful tuning of the steric environment around the C1–C2 olefin, the synthetically challenging pseudoequatorial dichlorides might be installed preferentially via substrate control. Eventually, in an attempt to accomplish deoxochlorination of 15 with SOCl$_2$, we unexpectedly found that the reaction afforded sultine 29, 16 less sterically hindered than the α-face. Therefore, the chloride cation approached the C1–C2 olefin from the β-face, and the resulting β-chloronium ion was attacked by chloride at the less hindered C2 position from the α-face to deliver 27 as the main product. Desulfination of 27 could be achieved under acidic and basic hydrolysis conditions, and heating a solution of 27 in DMF with TiCl₄ and LiCl was found to be optimal, affording 22 in 79% yield. Deoxochlorination of the C19 hydroxyl group of 22 (PPh₃, CCl₄) then furnished trichloride 28. Although we were able to introduce the C5–C6 olefin by using m-iodobenzoic acid and Ph₃Se$_2$ to give 29, attempts to desaturate 29 to access 1 failed under various conditions. Accordingly, we sought to install a hydroxyl group at C3 to facilitate late-stage introduction of the C3–C4 olefin.

**Scheme 3. Investigation of the olefin dichlorination reaction and subsequent transformations.**

To this end, olefin 16 was oxidized with SeO$_2$ to furnish allylic alcohol 17 as a single diastereomer (Scheme 2). Dichlorination of 17 with 3.3 equiv of Et$_2$NCI produced a 62% yield of dichloride 18, the structure of which was unambiguously established by X-ray crystallographic analysis. Alternatively, adding 17 to a solution of 8.0 equiv of Et$_2$NCI in dichloromethane (reverse addition method) delivered trichloride 19 and dichloride 18 in 61% and 19% yields, respectively. Notably, the successful chlorination at C16 to afford 19 was an encouraging result in that it suggested that conversion of clionastatin A to clionastatin B via direct C(sp$^3$)–H chlorination might be possible. Moreover, 19 could also be utilized for the synthesis of clionastatin B by means of the sequence used for the synthesis of clionastatin A from 18.

To complete the synthesis, we protected the C3 hydroxyl group of 18 as an acetate and then desulfinated the protected compound to generate 20. Deoxochlorination of 20 and subsequent desaturation (m-iodobenzoic acid, Ph$_3$Se$_2$) delivered trichloride 21 smoothly, after in situ hydrolysis of the C3 acetate. Finally, dehydration of 21 with Martin sulfurane to introduce the C3–C4 olefin completed the synthesis of clionastatin A (1). Pleasingly, regioselective chlorination of 1 at C16 with Et$_2$NCI using the reverse addition method for the synthesis of 19 delivered clionastatin B (2) in 42% yield, along with a 45% yield of recovered 1. The $^1$H NMR data for our synthetic 1 and 2 were in good agreement with those reported for the natural isolates (see Supporting Information for a discussion of some discrepancies in the $^{13}$C NMR data). However, nuclear Overhauser effect spectroscopy of 1 and 2 showed strong correlation between the C18–Me and the C14–H, which indicates...
that the C14–H was actually in the β-configuration rather than the originally proposed α-configuration. This configuration was unambiguously confirmed by X-ray crystallographic analysis of 1. That is, the C/D-ring system of the clonastatins is in fact in a cis-fused arrangement.

In conclusion, we have achieved the first total synthesis of clonastatins A and B, which was accomplished asymmetrically in 16 and 17 steps, respectively. The core tetracyclic framework was assembled through a radical fragment coupling reaction and an intramolecular Heck reaction. The C10 quaternary stereocenter was installed efficiently by means of a traceless stereochemical relay strategy. Furthermore, substrate-controlled diastereoselective olefin dichlorination of a sulfine intermediate was used to introduce the synthetically challenging C1 and C2 pseudoquaternary dichlorides. Our work also revealed that the true structures of clonastatins A and B are in fact the C14 epimers of the originally proposed structures.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data for all new compounds (PDF)

X-ray crystallographic data for 1 (CIF) (CCDC 2092061)

X-ray crystallographic data for 18 (CIF) (CCDC 2092062)

X-ray crystallographic data for 24 (CIF) (CCDC 2092063)

X-ray crystallographic data for 25 (CIF) (CCDC 2092064)

X-ray crystallographic data for 29 (CIF) (CCDC 2092065)

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Notes

The authors declare no competing financial interests.

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REFERENCES


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(15) For selected recent examples of natural product synthesis using the fragment coupling, see refs 15 and 16: Han, A.; Tao, Y.; Reisman, S. E. A 16-step synthesis of the isorcanoyldi nepetine (+)-perseanol. Nature 2019, 573, 563-567.


