Total Synthesis and Structure Revision of Halioxepine

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Abstract: The first total synthesis of halioxepine is accomplished using a 1,4-addition for constructing the quaternary center at C10 and a halo etherification for the generation of the tertiary ether at C7. The correct structure of halioxepine was determined by assembling different enantiomeric building blocks and by changing the relative configuration between C10 and C15.

Halioxepine (1) is a new meroditerpene isolated from the Indonesian sponge Haliclona sp. by Tanaka and co-workers in 2011.[1] It shows moderate cytotoxic and antioxidant activity and the structure was determined to comprise a hydroquinone, a tetrahydrooxepine and a cyclohexene moiety. The major challenge in the structure elucidation was the fact that the hydroquinone-tetrahydrooxepine and the cyclohexene spin systems were difficult to relate to each other. Consequently, there was some degree of uncertainty about the relative configuration of both regions with respect to each other so that two possible relative configurations were proposed: 1S*,2S*,7R*,10S*,15R* or 1S*,2S*,7R*,10R*,15R*. In 2018, the group of Rodriguez[2] reported two additional halioxepins, namely halioxepine B (2) and C (3) (Figure 1). In addition to NMR-experiments, they used DFT calculations to determine the stereochemical relationship of the two stereoclusters separated by two methylene units (C8, C9). Their analysis suggested 1S*,2S*,7R*,10R*,15R* to be the relative configuration of halioxepine (1) (Figure 1). In addition, they confirmed for halioxepine C (1) the absolute configuration at position C1 with the aid of the Mosher[3] ester method.

In the course of our ongoing program of accessing natural products through total synthesis,[4] we started the synthesis of halioxepine with the aim of confirming its proposed structure and to access this family of natural products for further biological investigation. Retrosynthetically, the stereoselective addition of the hydroquinone moiety should take place in the endgame of the synthesis and take advantage of the stereochemical controlling properties of the alpha chiral center. The tetrahydrooxepine ring should be constructed via an iodine-mediated ether formation which leads back to fragments 4 and 5. Compound 5 in turn, which should allow access to both, the syn- and anti-configured tetrahydrooxepine, can be assembled from Weinreb amide 6 and iodide 7. Both fragments can be obtained rapidly from simple starting materials 8, 9 and 10 (Scheme 1).

The synthesis of fragment 6 commenced with an enantioselective 1,4-addition[5] followed by acylation and subsequent methylation as reported by Herzon.[6] This sequence already generated the two chiral centers of this fragment in very high purity.

Figure 1. Proposed structures of the halioxepines. For halioxepine (1) and halioxepine B (2) only the relative configuration was proposed.

Scheme 1. Retrosynthetic analysis of halioxepine.
selectivities and 61% yield over three steps. Addition of methyl magnesium bromide and subsequent elimination using pTsOH established the trisubstituted double bond between C11 and C12. The ester was reduced to its corresponding alcohol using LiAlH₄ and finally, IBX oxidation followed by HWE-olefination introduced the two carbons which will separate the two chiral clusters (Scheme 2).

The synthesis of eastern fragment 7 started with aldehyde 9 which was converted to its corresponding Z-vinyl iodide 16 using a Zhao-Stork olefination. Subsequent halide-metal exchange generated the nucleophile which was added to aldehyde 10 to generate a racemic mixture. Allylic alcohol 17 was oxidized using IBX and selectively reduced with (+)-DIPCl to obtain the required Z-configured allylic alcohol in good yields and selectivities. TES protection and transformation of the PMB ether to its corresponding iodide completed the synthesis of eastern fragment 7 (Scheme 3).

The fragment coupling started with the halide-metal exchange of iodide 7 and addition to Weinreb amide 6. The desired α,β-unsaturated ketone 19 was formed in good yield along with small amounts of undesired ketone 25. Optimization of the reaction conditions partially led to suppression of byproduct formation, but only with diminishing yield of 19. As the byproduct could be removed during further steps, the conditions shown were applied. For reduction of the α,β-unsaturated ketone, different conditions were investigated (e.g. Stryker’s reagent, Raney-Ni, DiBAIH + HMPA + Cu + MelI) but only the combination of Co(acac)₂ and DiBAIH gave full conversion. Subsequent Wittig olefination and removal of the TES protecting group provided the starting material for the tetrahydrooxepine cyclization. This was accomplished with (2,4,6-collidine)PF₆ to provide a non-separable mixture of the syn and anti-isomers (syn:anti = 1:2.1). Removal of the terminal iodide was achieved with “super hydride” (LiEt₃BH) and the primary TBS group was removed with TBAF, which made separation of both diastereomers possible. At this stage N-oxe experiments could unambiguously identify the syn-tetrahydrooxepine which was part of the proposed structure. For the endgame of the synthesis, an aldol-type addition of TBS hydroquinone 23 to aldehyde 24 was envisioned. For this, alcohol syn-22 was oxidized and treated with a magnesium salt derived from deprotonation of mono-protected hydroquinone 23. The addition proceeded with high selectivity for the expected syn-diol which is proposed to proceed via a chelation-controlled transition state. Removal of the remaining TBS group with the aid of TBAF led to target molecule 1 (Scheme 4). Unfortunately, the NMR spectra significantly deviated from the ones of the authentic material (see Figure 3 and the Supporting Information).

Since the isolation papers covered in detail the relative orientation of both stereocenters to each other, we believed that the differences in the NMR spectra were the result of the opposite relative orientation of both stereocenters. As the configuration of the eastern hemisphere depends on the configura-
At C2 we reoxidized intermediate (S)-20 and reduced\(^{[1]}\) the \(\alpha,\beta\)-unsaturated ketone with (−)-DIPCl. With the so obtained inversion at C2 the steps carried out for the former isomer were repeated. Fortunately, the cyclization proceeds with higher selectivities (syn:anti = 2.3:1) and the aldol-type addition of hydroquinone gave again good yields and selectivities for diol 28 (Scheme 5). TBAF-mediated removal of the TBS group provided iso-halioxepine 29. However, even the NMR spectra of this isomer did not match the ones of the authentic material. So the problems in the configurational assignment were obviously not solved by changing the stereocenters.

A closer look into NMR spectra of compounds with fragments similar to the cyclohexene-fragment revealed, that there is a significant difference in \(^1\)H- and \(^13\)C-shifts for different relative orientations of the methyl groups corresponding to C20 and C18 (compare Figure 2, top).\(^{[18]}\) Comparing those shifts to the ones of authentic halioxepine and the synthesized isomers 1 and 29 (Figure 2, bottom), we suggest a syn-relationship of Me-20 and Me-18 for authentic halioxepine. Consequently, our next target was the proposed structure but with an inverted configuration at the quaternary carbon at C10.

The synthesis of the new western hemisphere (C7–C15) required a slightly altered route. Again, an asymmetric 1,4-addition was performed generating a 1.3:1 isomeric mixture of bis-methylated compound 31.\(^{[31]}\) However, the isomeric mixture was inconsequential as subsequent enamine formation and 1,4-addition led to stereoselective formation of the quaternary center.\(^{[19]}\) The ester and the keto-carbonyl groups were reduced and the primary alcohol was TBDPS-protected.\(^{[20]}\) Then, the secondary alcohol was re-oxidized and methyl addition followed by elimination generated the double bond in an endo- and exo-mixture. This was isomerized to the desired endo-olefin with rhodium(III)-chloride,\(^{[21]}\) which also removed the silicon protecting group (Scheme 6).

Oxidation of the so generated primary alcohol set the stage for coupling with eastern segment 7. As a byproduct alcohol 42 was formed, but it could be removed during further steps. Alcohol 35 was then oxidized and transformed to its corre-

### Scheme 5. Synthesis of iso-halioxepine 29 (o2s = over two steps).

### Scheme 6. Synthesis of altered western fragment 34, coupling with eastern fragment 7 and synthesis of iso-halioxepine 41 (o2s = over two steps, o3s = over three steps).
sponding exo-methylene derivative. At this stage, PPTS removed selectively the TBS group in the presence of the TBS group. As in the synthesis of the previous isomers, treatment with [2,4,6-collidine]PF$_6$ induced the tetrahydrooxepine formation in favor of the desired isomer with a 1.6:1-ratio. After TBAF deprotection, both isomers could be separated and alcohol 39 was oxidized and transformed in the above mentioned aldol-type addition of mono-protected hydroquinone 23. Finally, TBAF-mediated removal of the remaining TBS group provided compound 41 which again did not exhibit matching NMR spectra. However, analyzing the NMR signals derived from the methyl groups at C17, C18 and C20 we could clearly see that these are in better agreement with the ones of the authentic material (Figure 3).

Nevertheless, it could still be that we had to switch the relative configuration of the two stereocenters in relation to each other. This we could achieve by oxidizing alcohol (S)-37 and reducing the so obtained ketone with (-)DIPCI. The desired allylic alcohol (R)-37 was obtained in very good yield and selectivity and the subsequent tetrahydrooxepine cyclization succeeded in 88% yield. Removal of the iodide was achieved by treatment with LiEt$_3$BH (85%). The final steps, namely the removal of the TBS group, oxidation followed by aldol-type addition (configuration at C1 was confirmed via Mosher ester analysis; see Supporting Information) and final deprotection provided isomer 46 which NMR spectra were in very good accordance with the ones of the authentic material (see Figure 3 and Supporting Information). However, the optical rotation value had the opposite sign as reported in the isolation papers. We therefore had synthesized the enantiomer of halioxepine (Scheme 7).

A comparison of the $^1$H-NMR spectra of the here described synthetic compounds with the one obtained from the authentic material is a clear indication of the refined configuration of the halioxepines. Additionally, even if the stereocenters are separated they obviously influence the chemical shifts significantly. It should be pointed out here that in retrospect the analysis looks quite conclusive, however, things are not so obvious if one does not have isomers for comparison.

![Figure 3. Comparison of the $^1$H-NMR shifts of the methyl groups of different halioxepine isomers to the one from natural halioxepine.](image)

In summary, we were able to complete the first total synthesis of halioxepine and by doing so to revise its configuration at C10. The synthesis takes advantage of an asymmetric 1,4-addition and stereoselective Michael addition to control the configuration at the quaternary center and the one at C15. The stereocenters of the eastern stereocenter are consecutively derived from a stereoselective DIPCI reduction of a prochiral ketone. The iodonium-induced ether cyclization occurred in modest selectivities of 1.6:1. However, both isomers could be separated easily on the subsequent stage. The final aldol-type addition of the mono-protected hydroquinone occurred with high selectivities (>19:1). In the light of these findings, it seems very likely that the configuration at C10 of halioxepine C also needs some additional examination. Due to the different carbon skeleton in halioxepine B, the situation is not as clear cut as for halioxepine and halioxepine C. Our ongoing investigation in this direction will be reported in due course.

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### Conflict of interest

The authors declare no conflict of interest.
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Assemble and reassign: The first total synthesis of halioxepine is presented, along with a structural revision. Due to two stereoclusters separated by two methylene groups, there was some uncertainty about the relative configuration for halioxepine. Mismatched spectroscopic data for both suggested structures caused a new analysis and led to reassignment of the relative configuration between C10 and C15 (see figure).