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COMMUNICATION

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 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: 1*S**,2*S**,7*R**,10*S**,15*S** or 1*S**,2*S**,7*R**,10*R**,15*R**. 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 1*S**,2*S**,7*R**,10*R**,15*R** 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.

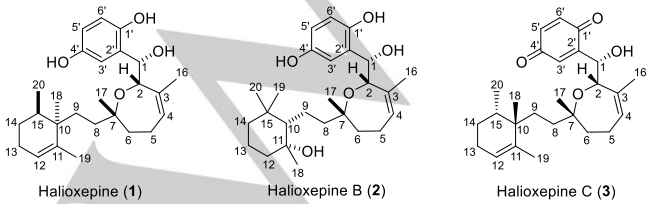
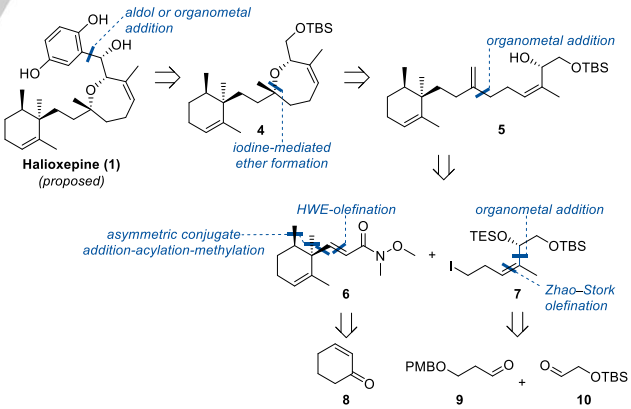


Figure 1. Proposed structures of the halioxepines. For halioxepine (**1**) and halioxepine B (**2**) only the relative configuration was proposed.

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. Retrosynthetic analysis of halioxepine.

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 selectivities and 61% yield over three steps. Addition of methyl magnesium bromide and subsequent elimination using *p*TsOH established

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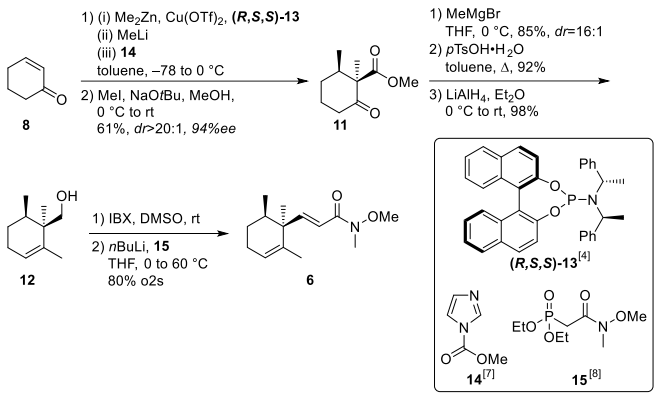
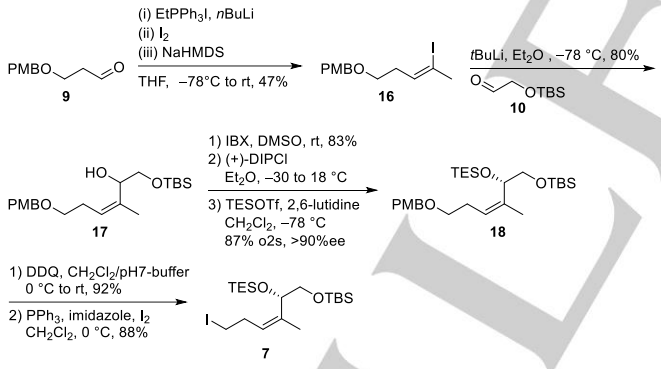
the trisubstituted double bond between C11 and C12. The ester was reduced to its corresponding alcohol using $LiAlH_4$ and finally, IBX oxidation followed by HWE-olefination introduced the two carbons which will separate the two chiral clusters (Scheme 2).



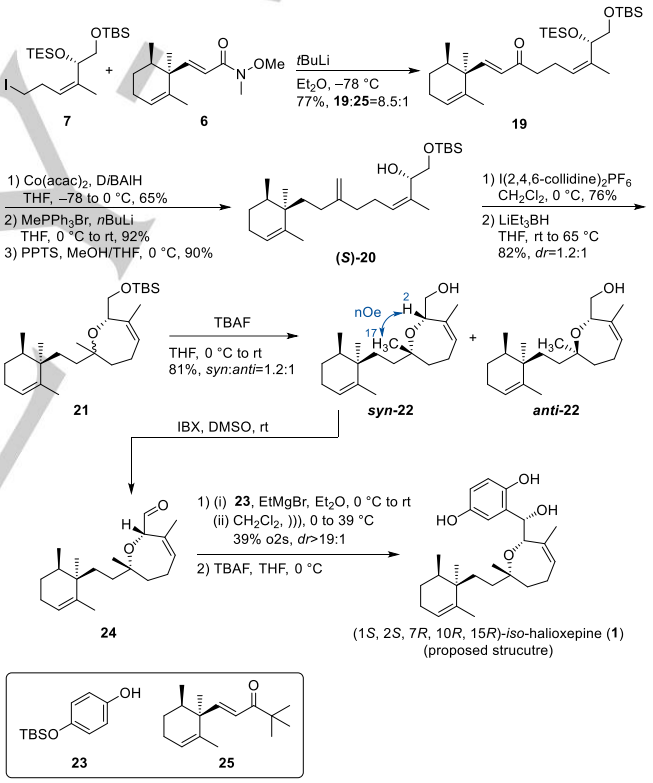
Scheme 2. Synthesis of western fragment **6** (o2s = over two steps).

The synthesis of eastern fragment **7** started with aldehyde **9**[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**[10] to generate a racemic mixture. Allylic alcohol **17** was oxidized using IBX and selectively reduced with (+)-DIPCl[3] 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).



Scheme 3. Synthesis of eastern fragment **7** (o2s = over two steps).

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. Strykers reagent,[11] Raney-Ni,[12] D*i*BAlH+HMPA+CuI+MeLi[13]) but only the combination of $Co(acac)_2$ and D*i*BAlH gave full conversion.[14] Subsequent Wittig olefination and removal of the TES protecting group provided the starting material for the tetrahydrooxepine cyclization. This was accomplished with $I(2,4,6\text{-collidine})_2PF_6$[15] 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" ($LiEt_3BH$) and the primary TBS group was removed with TBAF, which made separation of both diastereomers possible. At this stage nOe-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.[16] For this, alcohol ***syn*-22** was oxidized and treated with a magnesium salt derived from deprotonation of mono-protected hydroquinone **23**.[17] 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 SI).



Scheme 4. Coupling of both hemispheres and endgame of the synthesis of **1** (o2s = over two steps).

Since the isolation papers covered in detail the relative orientation of both stereoclusters to each other, we believed that the differences in the NMR spectra were the result of the opposite relative orientation of both stereoclusters. As the configuration of the eastern hemisphere depends on the configuration at C2 we reoxidized intermediate **(*S*)-20** and reduced[3] the α,β-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)

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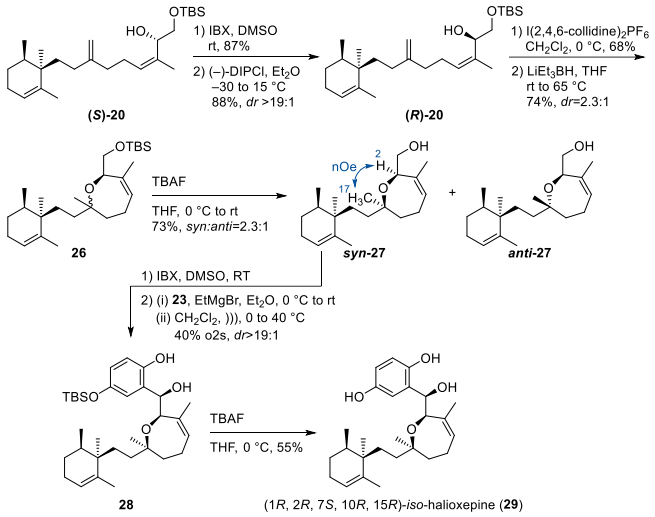
and the aldol-type addition of hydroquinone gave again good yields and selectivities for diol **28** (Scheme 5). TBAF-mediated removal of the TBS group provided *iso*-halioxepine **29**. However, even the NMR spectra of this isomer did not match the ones of the authentic material. So the problems in the configurational assignment were obviously not solved by changing the stereoclusters.



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

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.

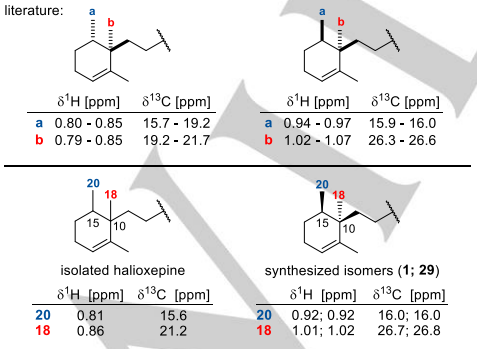
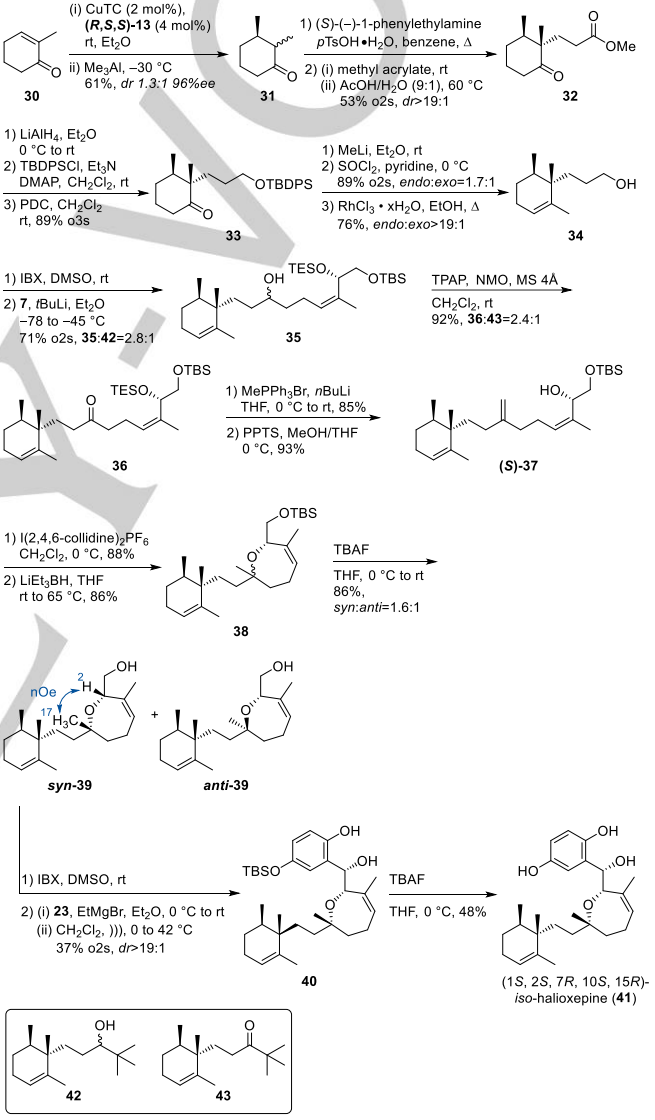


Figure 2. Comparison of ^{1}H- and ^{13}C-NMR shifts for cyclohexene-parts similar to those in halioxepine.

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**.[5] 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).



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).

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 corresponding *exo*-methylene derivative. At this stage, PPTS removed selectively the

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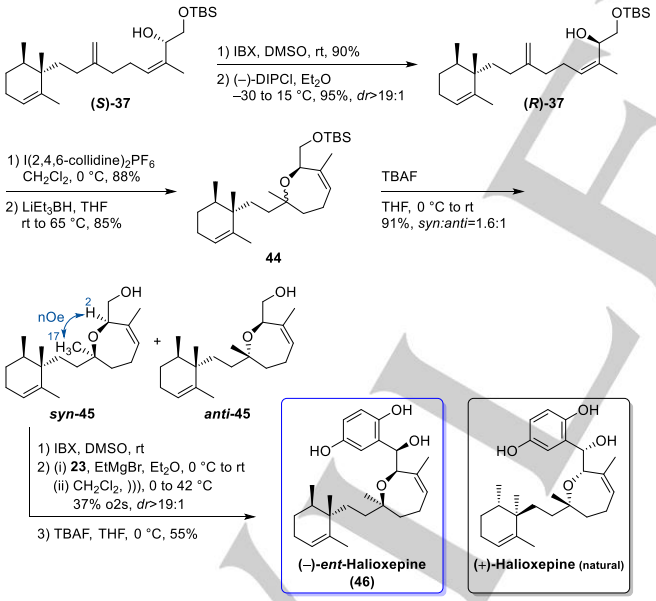
TES group in the presence of the TBS group. As in the synthesis of the previous isomers, treatment with $I(2,4,6\text{-collidine})_2PF_6$ induced the tetrahydrooxepine formation in favor of the desired isomer with a 1.6:1-ratio. After TBAF deprotection, both isomers could be separated and alcohol **39** 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 stereoclusters in relation to each other. This we could achieve by oxidizing alcohol **(*S*)-37** and reducing the so obtained ketone with (−)-DIPCl. The desired allylic alcohol **(*R*)-37**[3] 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 $LiEt_3BH$ (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;[3] see SI) 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 SI). 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. Endgame in the synthesis of *ent*-Halioxepine (**46**) (o2s = over two steps).

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 stereoclusters 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.

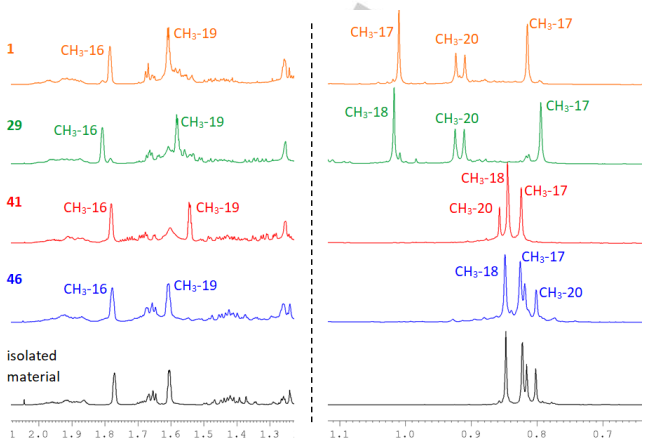


Figure 3. Comparison of the ^{1}H-NMR shifts of the methyl groups of different halioxepine isomers to the one from natural halioxepine.

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 stereocluster are consecutively derived from a stereoselective DIPCl 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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Keywords: halo etherification • natural product synthesis • quarternary stereocenter • structure elucidation • terpenoids

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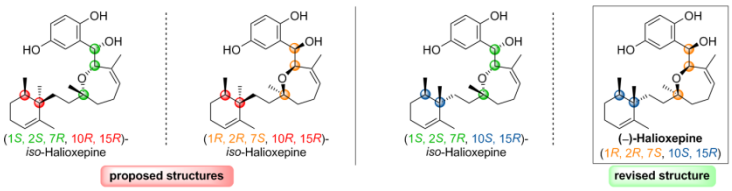

Assemble and reassign: The first total synthesis of halioxepine is presented, along with a structural revision. Due to two stereoclusters separated by two methylene groups, there was some uncertainty about the relative configuration for halioxepine. Mismatched spectroscopic data for both suggested structures caused a new analysis and led to reassignment of the relative configuration between C10 and C15.