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LETTERS

A Stereoselective One-Pot Synthesis of Perhydro-7a-hydroxy-7-phenylthiofurano[3,2-*b*]pyran *via* an Acid-catalysed Deprotection/Double Cyclisation/Rearrangement Sequence

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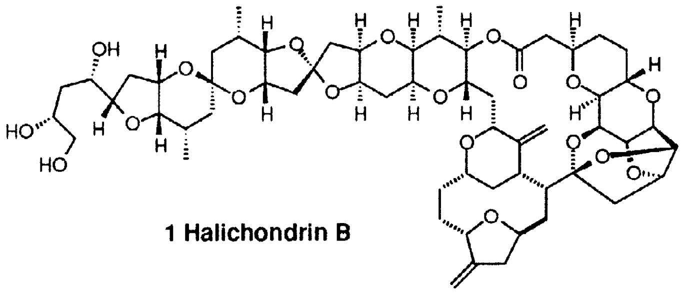
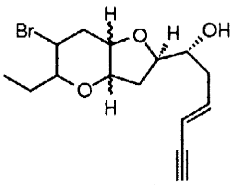
Abstract: Treatment of 1,3-*bis*-[(*tert*-butyldimethylsilyloxy)ethyl]-1-phenylsulfinyl-1,2-propadiene with aqueous HF in acetonitrile led to the formation of the title compound as one diastereoisomer (from NMR analysis). The reaction was carried out under thermodynamic conditions, and underwent a double deprotection/double cyclisation/rearrangement sequence.

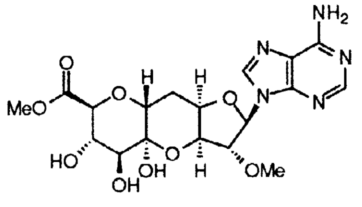
Polycyclic ethers feature widely in nature, and can be found, for example, in the marine metabolite halichondrin B (**1**),[1] in laurefucin (**2**),[2] and also in the nucleoside antibiotic herbicidin B (**3**).[3] Various strategies have been employed for the construction of such systems, including olefin metathesis[4] and hydroxy epoxide cyclisation,[5] and we have previously reported on the synthesis of 1,5-dioxadecalins from suitably functionalised allene sulfoxides.[6] We now wish to report on an extension of our allene sulfoxide chemistry, which we have used for the synthesis of a novel 1,4-dioxahydrindane, which was obtained as a single diastereoisomer under thermodynamic conditions.



1 Halichondrin B



2 Laurefucin



3 Herbicidin B

The formation of a single diastereoisomer was clear by NMR spectroscopy,[7] which also gave indications as to which isomer had been produced (*vide infra*).

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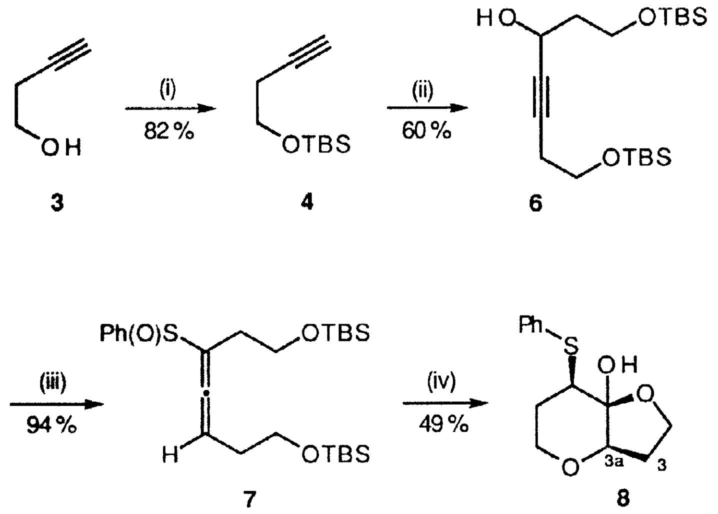
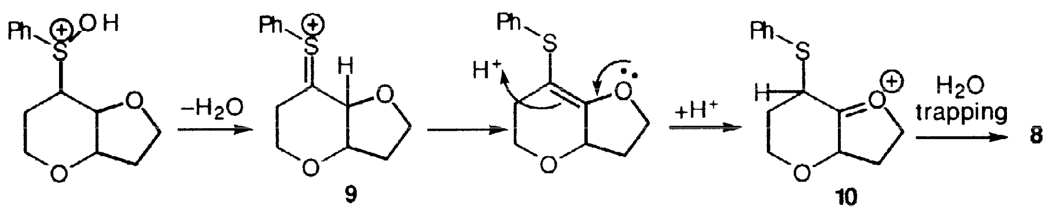
The route which was employed for the synthesis of the title compound is shown in Scheme 1. Commercially available 3-butyn-1-ol (**3**) was protected as the corresponding *tert*-butyldimethylsilyl ether (TBSCl, imidazole, DMAP, DMF)[8] (**4**) in 82 % yield. The acetylenic Grignard derived from (**4**) was prepared by exchange with ethylmagnesium bromide, and added to pre-prepared aldehyde (**5**),[9] affording propargylic alcohol (**6**) in 60 % yield. Treatment of (**6**) with benzenesulfenyl chloride,[10] in the presence of 1.5 equivalents of triethylamine, furnished allene sulfoxide (**7**) in 94 % yield. Finally, the requisite bicyclic polyether (**8**) was obtained in 49 % yield upon exposure of (**7**) to aqueous HF in acetonitrile.



Scheme 1. *Reagents & Conditions*: (i) TBSCl, imidazole, DMAP, DMF; (ii) EtMgBr, Et_2O then $OHCCH_2CH_2OTBS$ (**5**); (iii) PhSCl, Et_3N, Et_2O; (iv) aq HF, CH_3CN, 60 °C

The key step involves fluoride-induced desilylation of both silyl ethers, followed by acid-catalysed double cyclisation, and finally a Pummerer-type rearrangement, in which the sulfoxide moiety becomes protonated and undergoes subsequent dehydration to give thionium ion (**9**). A deprotonation and subsequent protonation occurs, producing oxonium ion (**10**) which is then trapped with water (Scheme 2).



Scheme 2

Proton NMR spectroscopy indicated that H-3a coupled to only one of the adjacent protons (H-3 or H-3') appearing as a doublet ($^3J_{3a,3}$=4.4 Hz). This finding prompted us to carry out molecular mechanics and geometry calculations, in order to discover which diastereoisomer had been synthesised. Firstly, the heats of formation of the *cis*- and the *trans*-fused isomers were calculated using an optimised geometry calculation in

MOPAC using AM1 (semi-empirical) parameters.[11] This indicated that the *cis*-fused diastereoisomer ($\Delta H_f(cis)$=–447.7 kJmol^{-1}) is significantly more stable than the *trans*-fused diastereoisomer ($\Delta H_f(trans)$=–415.1 kJmol^{-1}) so that under thermodynamic reaction conditions, it will be formed preferentially. The molecular mechanics calculations also suggested that the *cis*-fused isomer would be more stable, on comparison of the global conformational minima (175.5 kJmol^{-1} for *cis* versus 194.8 kJmol^{-1} for *trans*).[12] The -SPh moiety was, as expected, oriented equatorially, and the lowest energy conformations of the *cis* isomer were concerned with rotations of this group, rather than changes in the ring conformations. The exclusively formed diastereoisomer that was obtained is shown in Figure 1.

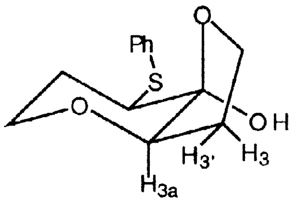


Figure 1

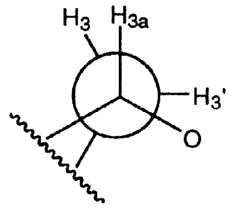


Figure 2

The calculated dihedral angles and coupling constants agreed with those observed by NMR spectroscopy ($\Phi_{3a,3}$=–30.6°, $^3J_{3a,3}$=6.1 Hz; $\Phi_{3a,3'}$=89.9°≈90°, $^3J_{3a,3'}\approx$0 Hz for global conformational minimum) and the dihedral angles and coupling constants calculated for higher energy conformations remained close to the observed values. Conversely, for the *trans* isomer, the dihedral angles were 37.8° and 159.6° respectively, both of which translate into significantly non-zero coupling constants. The Newman projection (Figure 2) shows the view down the C-3a–C-3 bond axis (*cis* isomer).

The conformation of the 6-membered ring is constrained by the presence of the -SPh group, which in the alternative conformer would be axial, leading to severe steric implications. The 5-membered ring conformation is presumably also constrained, since the alternative conformation would produce severe eclipsing interactions between the protons on C-2 and C-3.

In conclusion, we have reported a new synthesis of the 1,4-dioxahydrindane ring system, using a novel double deprotection-double cyclisation-rearrangement sequence mediated by aqueous HF in acetonitrile under equilibrating conditions. Only one diastereoisomer was observed by NMR spectroscopy, and we could conclude from this data, supported by molecular mechanics calculations, that this isomer was the one shown in Figure 1. We are currently investigating the scope of this tandem reaction within natural product synthesis, and will report further results in due course.

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