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The Absolute and Relative Configuration of Muamvatin

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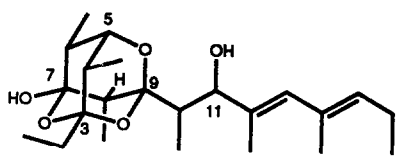
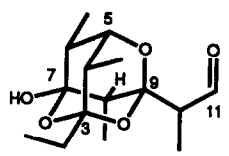
Abstract: Both epimers of the aldehyde 2, a degradation product of muamvatin, have been synthesized in a stereodefined manner. This allowed us to assign the relative and absolute configuration to muamvatin as shown in 19. Key to this synthesis was a novel chiral building block 10, representing the stereotriad D.

Muamvatin has been isolated from *Siphonaria normalis* by the group of C. Ireland.[1] They proposed structure **1** for this polyketide natural product on the basis of extensive NMR investigations. While the relative configuration at C4, C5, C6, C8 (for the numbering see below) could be deduced from the NMR spectra, the relative configuration at C10 and C11 remained unknown, as well as the absolute configuration. Upon degradation of muamvatin Ireland obtained the dextrarotatory aldehyde **2**. It therefore appeared possible to establish the configuration of muamvatin by a stereodefined synthesis of the aldehyde **2**. We suspected that the two C10 epimers of **2** might have very similar spectral properties. For this reason we felt it necessary to synthesize both C10 epimers of **2**, in order to render the structural assignment of **2** unambiguous.

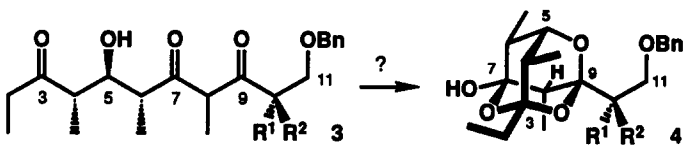


1



2

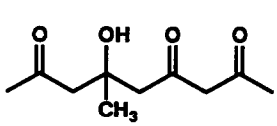
The conspicuous structural element of muamvatin is the hydroxy-trioxaadamantane unit **4**. This polycyclic system is expected to arise by cyclisation of a hydroxy-tricarbonyl compound **3**. In fact, such a cyclisation (**5** → **6**) had previously been realized by H. Agback.[2]



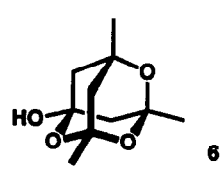
3

4

3a,4a: $R^1 = CH_3$; $R^2 = H$
3b,4b: $R^1 = H$; $R^2 = CH_3$

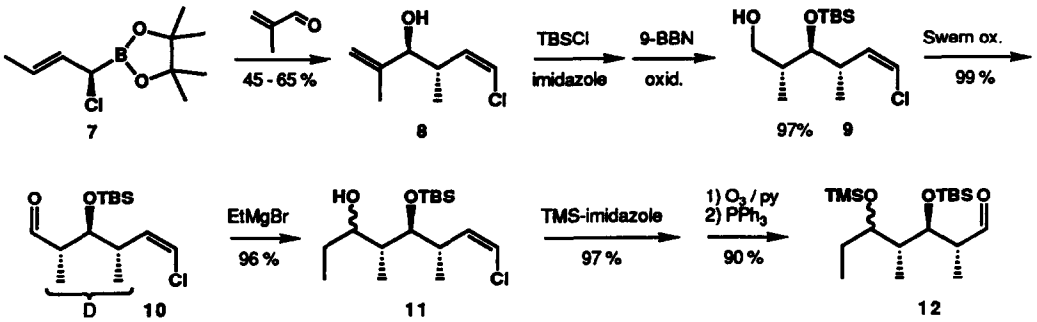


5



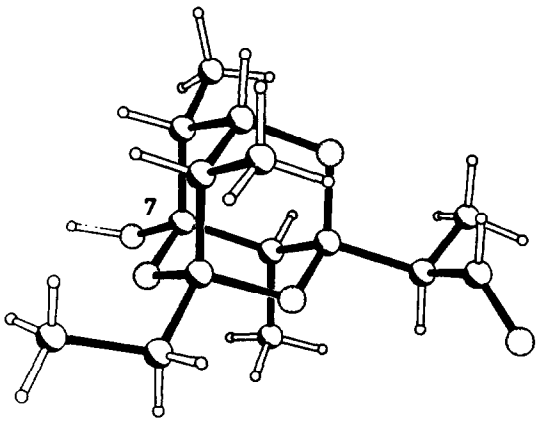
6

With this precedent in mind we embarked on a synthesis of **3**. The starting point was the (R)-α-chlorocrotylboronate **7**.[3] Reaction with methacrolein led to the homoallyl alcohol **8** of 96% diastereomeric purity and 90% e.e. After protection of the hydroxyl group as a t-butyldimethylsilyl ether the 1,1-disubstituted double bond was selectively hydroborated to furnish alcohol **9**.[4] Swern oxidation generated the aldehyde **10**, which is a readily accessible and versatile chiral building block[5] for the synthesis of natural products containing the stereotriad D.[6] Addition of ethylmagnesium bromide to **10** resulted in a 7:1 mixture of alcohols **11**, which were protected as trimethylsilyl ethers. Ozonolysis of the vinyl chloride function in the presence of pyridine provided the aldehyde **12**.



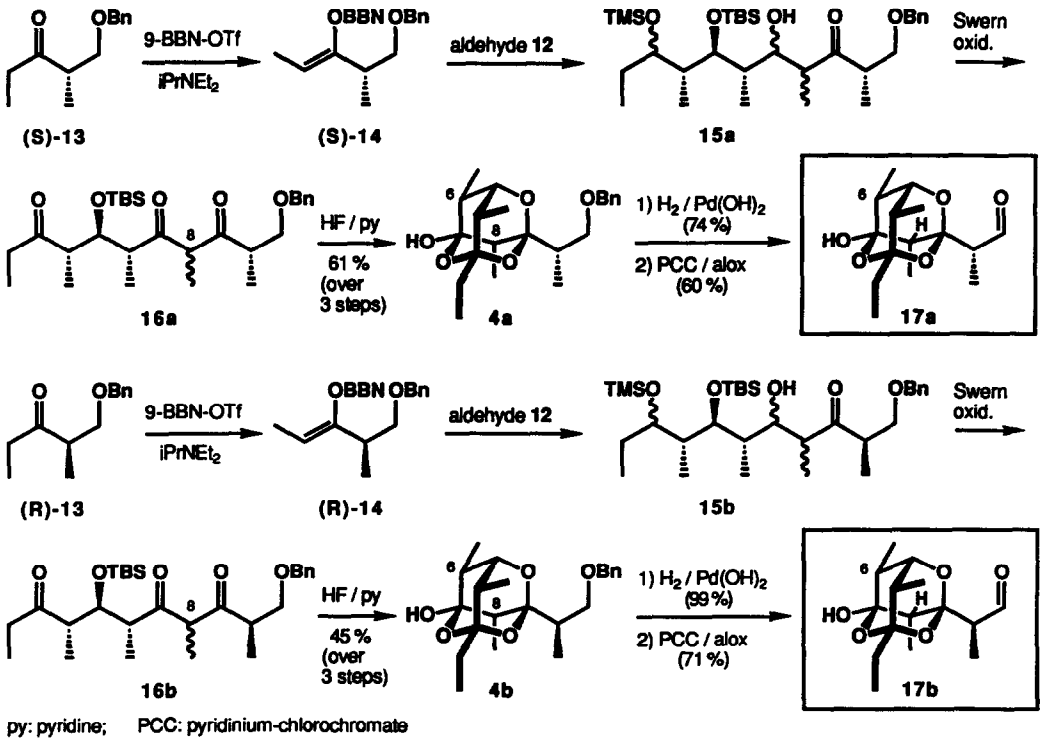
TBS: t-butyldimethylsilyl; 9-BBN: 9-borabicyclo(3.3.1)nonane; TMS: trimethylsilyl

At this point the synthon **12** had to be connected to each of the enantiomeric C8-C11 fragments **13**. The benzyloxy ketones **13** are readily accessible[7] from the commercially available, enantiomerically pure, 3-hydroxy-isobutyrates. Condensation of the aldehyde **12** with either enantiomer of **13** via the 9-BBN-enolborinates **14** proceeded according to the precedent given by I. Paterson's studies.[7] The resulting ketols **15** were not isolated but directly oxidized under Swern conditions. Apparently the hydroxy group at C7 as well as the trimethylsilyloxy group at C3[8,9] are both converted to alkoxy-sulfonium intermediates (the TBS-group is inert under these conditions[9]) and oxidized to ketones without intervention of a δ-hydroxyketone intermediate. The latter would have been expected to cyclize to a pyranose derivative, preventing oxidation to a 1,5-diketone. Without isolation of the intermediate triketones **16**, the TBS-protecting group was removed by treatment with pyridinium fluoride in THF to liberate the hydroxy-triketone **3**. A small amount of water was needed to initiate the immediate formation of the trioxaadamantane skeleton **4**.



X-ray crystal structure of **17a**.
The carbonyl group hydrogen bonds to C7-OH of the next molecule

(The crystal data, atomic coordinates etc. have been deposited with the Cambridge Crystallographic Data Center.)

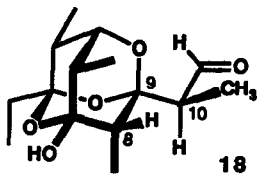


At the stage of the triketones **3** and **16** the configuration at C8 is labile. The cyclization to **4** occurs under thermodynamic control and leads to that C8-epimer of **4** in which the methyl group at C8 avoids a g^+g^--interaction with the C6-methyl group. This happens to be the correct configuration at C8.

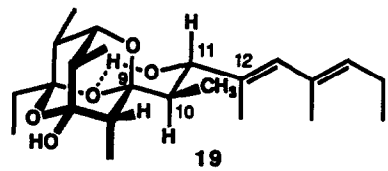
With the trioxaadamantane skeleton in place, hydrogenolytic cleavage of the benzyloxy group at C11 and subsequent oxidation generated each of the two epimeric aldehydes **17**. The 10(R)-aldehyde **17a** crystallized (m.p. 153 - 164°C) and permitted the verification of the relative configuration by an X-ray crystal structure determination. The ^{1}H NMR spectra of **17a** and **17b** were almost identical. The only significant difference is the signal of the aldehyde proton **17a**: δ = 10.04 (s); **17b**: δ = 9.71 (d, J = 2.6 Hz). Likewise the 75 MHz ^{13}C NMR spectra showed only small but sufficiently characteristic differences.

17a: δ =	5.8; 6.7; 7.0; 13.1; 13.4; 29.6; **34.4**; 37.5; 43.2; 50.5; 79.0; 97.3; **103.0**; 103.1; 203.3
2[1]: δ =	5.8; 6.6; 7.0; 13.1; 13.4; 29.6; **34.4**; 37.4; 43.1; 50.5; 78.9; 97.2; **103.1**; *105.4*; 203.3
17b: δ =	5.8; 7.0; 7.4; 13.1; 13.4; 29.6; **36.2**; 37.6; 43.0; 51.9; 79.0; 97.3; **101.2**; 102.6; 202.6

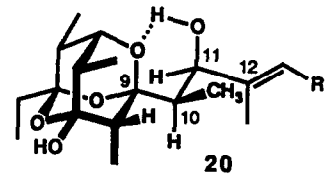
These data indicate that the muamvatin derived aldehyde **2** has the same relative configuration as **17a**. The signal reported[1] for **2** at 105 ppm could be due to residual muamvatin in the sample. The rotation of **17a**, $[\alpha]_D^{20}$ = -75.6 (c = 3.19, CH_2Cl_2) is opposite in sign to that reported for **2**: $[\alpha]_D^{25}$ = +50.2 (c = 0.0917, CH_2Cl_2). The structure of **2** must therefore be as shown in **18**.



18



19



20

In **18**, only the indicated conformation of the C9/C10-bond avoids a g^+g^--interaction between the substituents at C10 and the C8-methyl group. The aldehyde group then takes up a conformation pointing away from the net dipole of the acetal moiety. This brings the H11-C11-C10-H10-dihedral angle close to 90° in agreement with the vanishing ^3J-coupling constant found. Knowledge of the relative configuration at C-10 now allows the assignment of the relative configuration at C11 in muamvatin: The two possibilities are the *anti*-isomer **19** and the *syn*-isomer **20**. As a consequence of conformational restraints due to avoidance of g^+g^--interactions[10] between the methyl groups at C8, C10 and C12, the preferred conformation in each case should be those shown as **19** and **20**. In **19** this results in a *trans*-arrangement of H10 and H11 and therefore in a large coupling constant for these protons in the ^{1}H NMR spectrum. In turn, this coupling constant should be small in the isomer **20**. The value reported by Ireland,[1] 9.0 Hz, indicates, that muamvatin is the *anti*-isomer **19**. The same conclusion has been recently reached in an independent study by I. Paterson.[11]

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