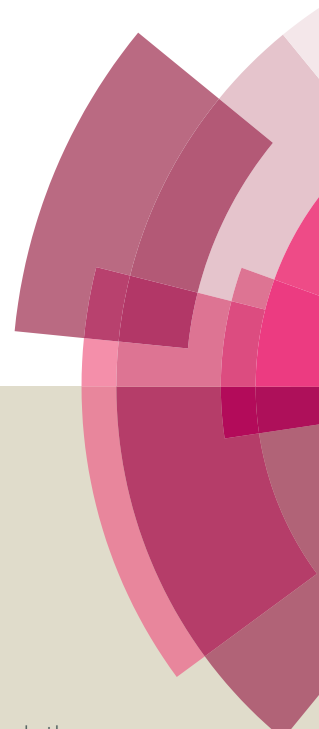
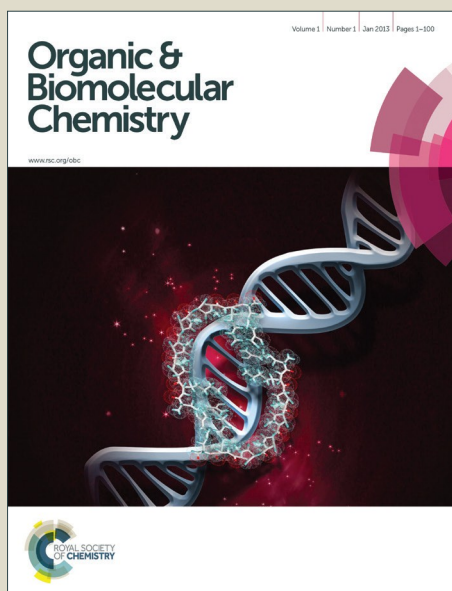


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ARTICLE

A Protecting Group-Free Synthesis of (-)-Hortonones A-C from the Inhoffen-Lythgoe Diol

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Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

A synthesis of hortonones A-C has been accomplished from Vitamin D₂ *via* the Inhoffen-Lythgoe diol without the use of protective groups. Key steps in the syntheses include a TMS-diazomethane mediated regioselective homologation of the cyclohexanone ring to a cycloheptanone moiety and a sodium naphthalenide-mediated allylic alcohol transposition. It has been found that the absolute configuration of the natural hortonones is opposite that of the synthetic material prepared from Vitamin D₂.

Introduction

The hexahydroazulenones hortonones A-C (Figure 1) are a series of rearranged sesquiterpenoids isolated by Andersen et al. in 2011 from the leaves of Sri Lankan *Hortonia*.¹ Importantly, hortonone C showed *in vitro* cytotoxicity against human breast cancer MCF-7 cells at 5 µg/mL. A short synthetic route to these compounds would facilitate further investigation of their biological properties and allow for the preparation of derivatives with enhanced antitumor activities. In addition, total synthesis would allow a confirmation of the relative and absolute stereostructure of these natural products.

We envisioned that the Inhoffen-Lythgoe diol,² a *trans*-fused 6,5 ring system possessing an array of contiguous stereocenters readily available either from ergocalciferol (vitamin D₂) by exhaustive oxidative cleavage³ or by asymmetric synthesis,¹⁸ was an ideal synthetic precursor of the hortonones. Acid- or base-mediated isomerization of the easily derived ketone **5** would give the *cis* ring fusion present in the hortonones. Subsequent ring homologation, dehydrogenation, and 1,3-enone transposition would give hortonone C; hortonones A and B then could be derived from hortonone C by organometallic 1,2-addition followed by 1,3-oxidative transposition (Figure 2).

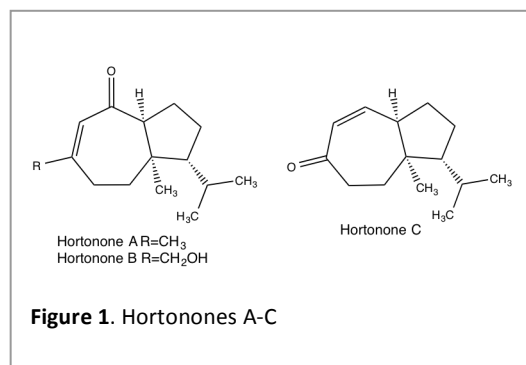


Figure 1. Hortonones A-C

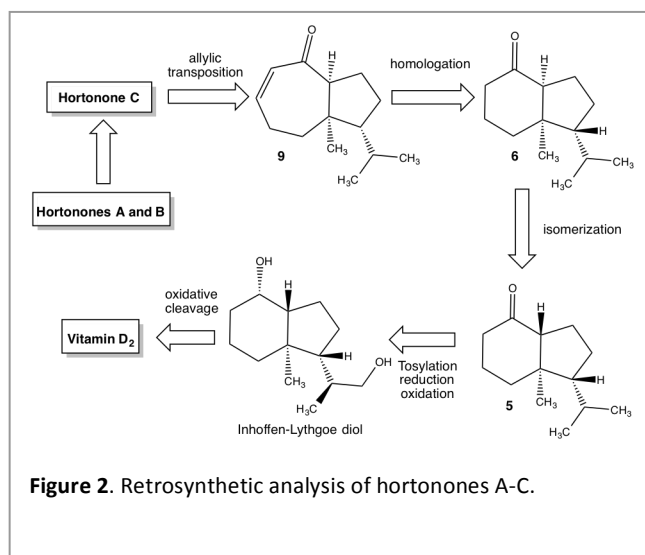


Figure 2. Retrosynthetic analysis of hortonones A-C.

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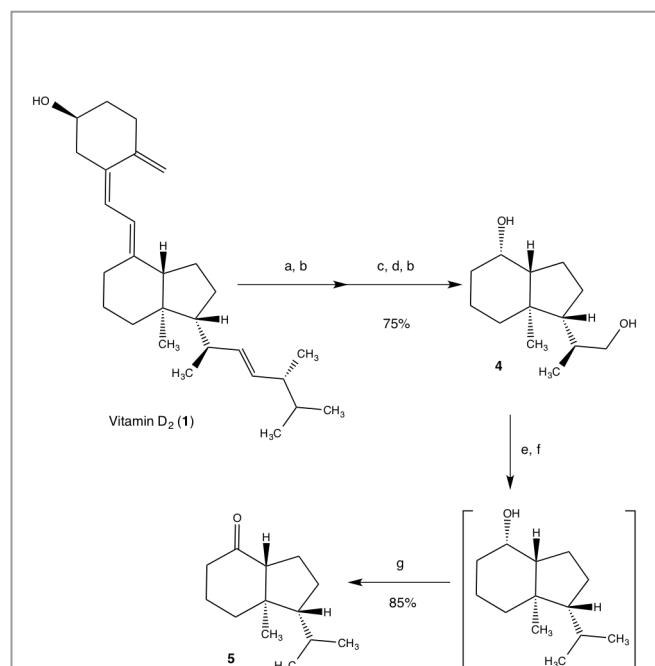
[†] Electronic Supplementary Information (ESI) available: Experimental procedures and characterization data for all new compounds; ¹H and ¹³C NMR spectra for all compounds in Schemes 1-4. See DOI: 10.1039/x0xx00000x

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Results and Discussion

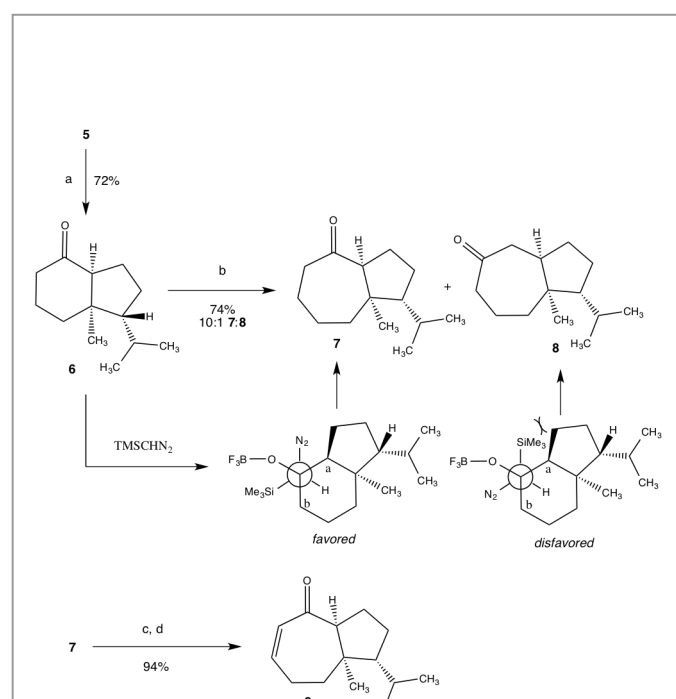
Oxidative cleavage of ergocalciferol with ozone (1:1 CH₂Cl₂/CH₃OH) followed by reductive workup with NaBH₄ afforded low overall yields (~40%) of the Inhoffen-Lythgoe diol in our hands.³ However, subjecting the crude ozonolysis product mixture to catalytic dihydroxylation (1 mol % OsO₄, NMO, acetone/H₂O),⁴ oxidative cleavage (KIO₄, dioxane/H₂O) and reduction (NaBH₄/MeOH) gave the desired diol **4** in 75% overall yield (Scheme 1). Transformation to the intermediate ketone **5** was then achieved in 85% yield by a three-step sequence involving selective tosylation of the primary alcohol, reduction of the tosylate with LiAlH₄, and oxidation of the secondary alcohol with Dess-Martin Periodinane.⁵



Scheme 1. Synthesis of intermediate **5**. *Reagents and conditions:* (a) O₃, CH₂Cl₂, MeOH, -78 °C; (b) NaBH₄, MeOH, rt, 20 min; (c) 1 mol% OsO₄, NMO, acetone, H₂O, rt, 5h; (d) KIO₄, 1:1 dioxane/H₂O, rt, 3h; (e) TsCl, Et₃N, DMAP, CH₂Cl₂, rt, 1h; (f) LiAlH₄, THF, rt, 5h; (g) Dess-Martin Periodinane, CH₂Cl₂, rt, 1h.

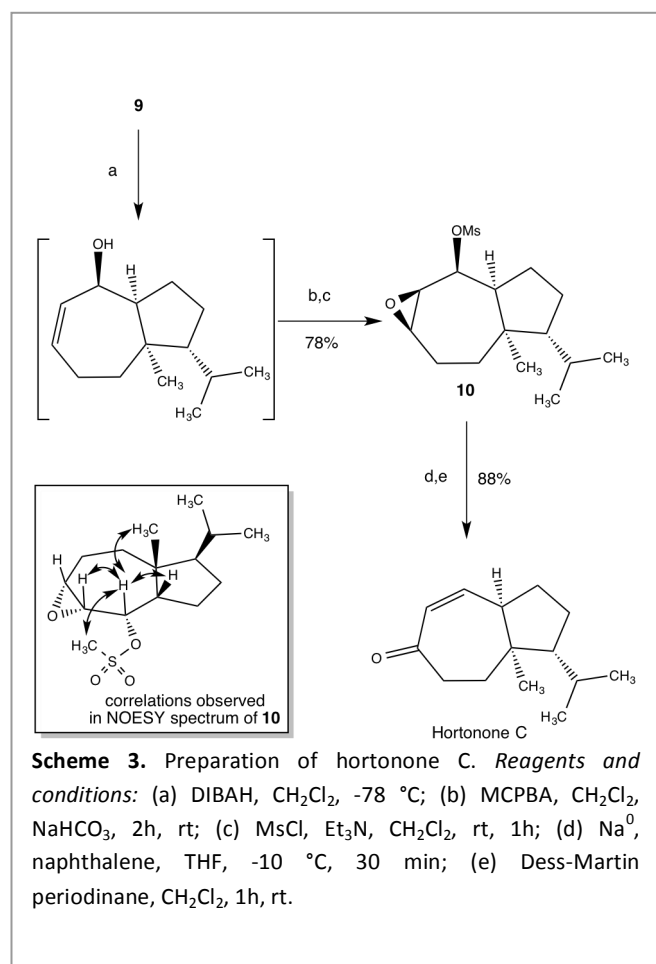
The *trans*-fused ketone **5** was then subjected to isomerization under basic conditions (NaH, THF, reflux, 4 h)⁶ to provide the corresponding *cis* ketone **6** in 72% yield after chromatography (Scheme 2). Initial attempts at homologation of this ketone to the 7-5 ring system of the hortonones by cyclopropanation of the kinetic trimethylsilyl enol ether of **6** and oxidative cleavage

with FeCl₃ were unfruitful.⁷ Furthermore, reduction of the ketone to the corresponding alcohol and attempted elimination of the alcohol with Burgess reagent¹⁷ led to an inseparable mixture of alkene regioisomers. However, it was discovered that exposure of **6** to TMSCHN₂ and BF₃•OEt₂ in DCM at -40 °C followed by warming to room temperature provided the expanded ketone **7** in 74% yield with high regioselectivity (10:1 **7**:**8**).⁸ It is likely that approach of TMSCHN₂ to the activated carbonyl of **6** preferentially takes place in such a way as to minimize steric interactions between the bulky trimethylsilyl group and the cyclopentane ring of **6**. As a result, the favoured addition conformer (Scheme 2) places the alpha carbon atom "b" *anti* to the nitrogen leaving group, giving rise to cycloheptanone **7** as the major product upon rearrangement. Dehydrogenation of **7** was then accomplished by the Saegusa protocol (TBSOTf, Et₃N, CH₂Cl₂, 0° C, 2h; 50 mol % Pd(OAc)₂, CH₃CN, rt, overnight),⁹ affording enone **9** in 94% yield.

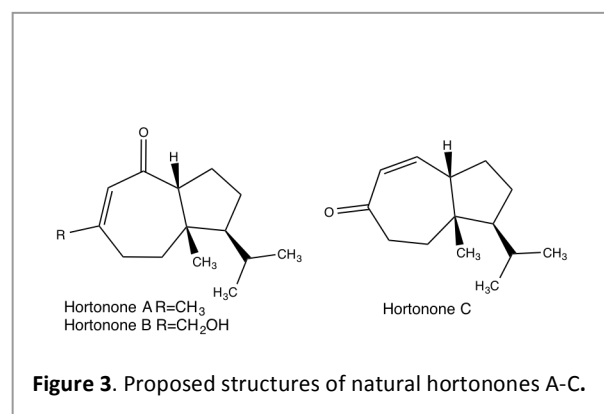
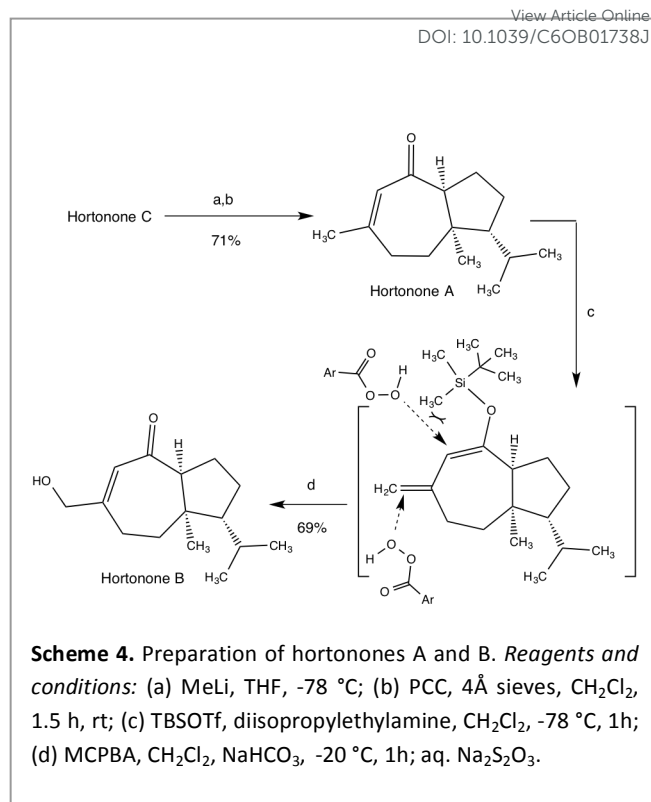


Scheme 2. Synthesis of *cis*-enone **9**. *Reagents and conditions:* (a) NaH, THF, reflux, 4h; (b) TMSCHN₂, BF₃•OEt₂, CH₂Cl₂, -40 °C – rt; (c) TBSOTf, Et₃N, CH₂Cl₂, rt, 2h; (d) 50 mol% Pd(OAc)₂, CH₃CN, rt, 12h.

Conversion of cycloheptenone **9** into hortonone C required a 1,3-enone transposition,¹⁹⁻²¹ the most utilized method for which is the protocol of Wharton.¹⁰ However, all attempts to transpose the enone of **9** by Wharton reaction of the corresponding epoxy ketone failed. Nonetheless, hortonone C could be secured by a sequence involving an allylic alcohol 1,3-transposition (Scheme 3).²² Reduction of **9** with DIBAH followed by stereoselective epoxidation and mesylation of the secondary alcohol afforded a 78% overall yield of **10**, the relative stereochemistry of which was confirmed by two-dimensional NMR (NOESY) experiments (See Scheme 3 and Supporting Information). Compound **10** was then reduced with a solution of sodium naphthalenide in THF (3M) at -10 °C to the corresponding allylic alcohol,¹¹ which was then oxidized with the Dess-Martin reagent⁵ to provide hortonone C in 88% yield. Spectroscopic data (¹H NMR, ¹³C NMR, MS, UV) for synthetic hortonone C were fully consistent with those reported for the natural sample by Anderson et al.¹ However, the specific rotation for our sample (-116.0) was in the opposite sense of that reported for natural hortonone C (+74).



Initial attempts to prepare hortonone A by conjugate addition of organocuprates (CH₃MgBr/CuI¹²; Me₂CuLi/TMSCl¹³) to enone **9** and oxidation of the resulting ketone afforded complex product mixtures and low overall yields. However, hortonone A could be easily prepared from hortonone C in



71% yield by methyllithium addition (ether, -78 °C) followed by oxidative transposition of the tertiary allylic alcohol with PCC (4Å sieves, CH₂Cl₂).¹⁴ Oxidation of hortonone A to hortonone B was accomplished in 69% yield by enolization (TBSOTf, DIPEA, -78 °C),¹⁵ regioselective epoxidation (1.1 equiv MCPBA, CH₂Cl₂, NaHCO₃, -20 °C) and aqueous hydrolysis (Scheme 4).¹⁶ Selective attack of the peracid at the less crowded exocyclic olefin of the dienolsilane intermediate appears to be favoured at lower temperatures. Again, all spectroscopic data for synthetic hortonones A and B closely matched those reported for the natural products, with the exception of the specific rotations (synthetic hortonone A: [α]_D -31.7; natural hortonone A: [α]_D +24.0; synthetic hortonone B: [α]_D -37.5; natural hortonone B: [α]_D +24.0).

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Conclusions

The synthesis presented here allows the preparation of all three hortonones in 12-15 steps from the readily available Inhoffen-Lythgoe diol. This study has revealed that the absolute configuration of the hortonones is opposite that originally proposed by Andersen et al. (Figure 3),¹ and thus vitamin D2 is not a likely biosynthetic precursor of this family of natural products. A synthetic route to (+)-hortonones A-C from an alternate starting material is currently being investigated and our findings will be reported in due course.

Acknowledgements

This communication is dedicated to Professor Peter B. Dervan on the occasion of his 70th birthday. The authors thank Jason Lee for his preparation of compound **4**. We acknowledge the National Science Foundation (CHE-1508070), the National Institutes of Health (SC3 GM 096899-01) and the donors of the American Chemical Society Petroleum Research Fund (53693-URI) for their generous support of this research.

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