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

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A synthesis of hortonones A-C has been accomplished from Vitamin D\textsubscript{2} 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 D\textsubscript{2}.

Introduction

The hexahydroazulenones hortonones A-C (Figure 1) are a series of rearranged sequiterpenoids isolated by Andersen et al. in 2011 from the leaves of Sri Lankan Hortonia\textsuperscript{1}. Importantly, hortonone C showed \textit{in vitro} cytotoxicity against human breast cancer MCF-7 cells at 5 \( \mu \)g/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\textsuperscript{2}, a \textit{trans}-fused 6,5 ring system possessing an array of contiguous stereocenters readily available either from ergocalciferol (vitamin D\textsubscript{2}) by exhaustive oxidative cleavage\textsuperscript{3} or by asymmetric synthesis\textsuperscript{18}, was an ideal synthetic precursor of the hortonones. Acid- or base-mediated isomerization of the easily derived ketone 5 would give the \textit{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).

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\textsuperscript{1} Electronic Supplementary Information (ESI) available: Experimental procedures and characterization data for all new compounds; \textsuperscript{1}H and \textsuperscript{13}C NMR spectra for all compounds in Schemes 1-4. See DOI: 10.1039/x0xx00000x
Results and Discussion

Oxidative cleavage of ergocalciferol with ozone (1:1 CH$_2$Cl$_2$/CH$_3$OH) followed by reductive workup with NaBH$_4$ afforded low overall yields (~40%) of the Inhoffen-Lythgoe diol in our hands. However, subjecting the crude ozonolysis product mixture to catalytic dihydroxylation (1 mol % OsO$_4$, NMO, acetone/H$_2$O), oxidative cleavage (KIO$_4$, dioxane/H$_2$O) and reduction (NaBH$_4$/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 LiAlH$_4$, and oxidation of the secondary alcohol with Dess-Martin Periodinane.

The trans-fused ketone 5 was then subjected to isomerization under basic conditions (NaH, THF, reflux, 4 h) 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 FeCl$_3$ were unsuccessful. Furthermore, reduction of the ketone to the corresponding alcohol and attempted elimination of the alcohol with Burgess reagent led to an inseparable mixture of alkene regioisomers. However, it was discovered that exposure of 6 to TMSCHN$_2$ and BF$_3$•OEt$_2$ 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). It is likely that approach of TMSCHN$_2$ 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, Et$_3$N, CH$_2$Cl$_2$, 0 °C, 2h; 50 mol % Pd(OAc)$_2$, CH$_3$CN, rt, overnight), affording enone 9 in 94% yield.

Scheme 1. Synthesis of intermediate 5. Reagents and conditions: (a) O$_3$, CH$_2$Cl$_2$, MeOH, -78 °C; (b) NaBH$_4$, MeOH, rt, 20 min; (c) 1 mol% OsO$_4$, NMO, acetone, H$_2$O, rt, 5h; (d) KIO$_4$, 1:1 dioxane/H$_2$O, rt, 3h; (e) TsCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, rt, 1h; (f) LiAlH$_4$, THF, rt, 5h; (g) Dess-Martin Periodinane, CH$_2$Cl$_2$, rt, 1h.

Scheme 2. Synthesis of cis-enone 9. Reagents and conditions: (a) NaH, THF, reflux, 4h; (b) TMSCHN$_2$, BF$_3$•OEt$_2$, CH$_2$Cl$_2$, -40 °C – rt; (c) TBSOTf, Et$_3$N, CH$_2$Cl$_2$, rt, 2h; (d) 50 mol % Pd(OAc)$_2$, CH$_3$CN, rt, 12h.
Conversion of cycloheptone 9 into hortonone C required a 1,3-enone transposition,\textsuperscript{19-21} the most utilized method for which is the protocol of Wharton.\textsuperscript{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).\textsuperscript{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,\textsuperscript{11} which was then oxidized with the Dess-Martin reagent\textsuperscript{12} to provide hortonone C in 88% yield. Spectroscopic data (\textsuperscript{1}H NMR, \textsuperscript{13}C NMR, MS, UV) for synthetic hortonone C were fully consistent with those reported for the natural sample by Anderson et al.\textsuperscript{1} However, the specific rotation for our sample (-116.0) was in the opposite sense of that reported for natural hortonone C (+74).

\begin{figure}[h]
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\includegraphics[width=\textwidth]{scheme3.png}
\caption{Scheme 3. Preparation of hortonone C. Reagents and conditions: (a) DIBAH, CH\textsubscript{3}Cl\textsubscript{2}, -78 °C; (b) MCPBA, CH\textsubscript{3}Cl\textsubscript{2}, NaHCO\textsubscript{3}, 2h, rt; (c) MsCl, Et\textsubscript{3}N, CH\textsubscript{3}Cl\textsubscript{2}, rt, 1h; (d) Na\textsuperscript{+}, naphthalene, THF, -10 °C, 30 min; (e) Dess-Martin periodinane, CH\textsubscript{3}Cl\textsubscript{2}, 1h, rt.}
\end{figure}

Initial attempts to prepare hortonone A by conjugate addition of organocuprates (CH\textsubscript{3}MgBr/Cu\textsuperscript{+}; Me\textsubscript{2}CuLi/TMSCLi\textsuperscript{13}) 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, CH\textsubscript{3}Cl\textsubscript{2}).\textsuperscript{14} Oxidation of hortonone A to hortonone B was accomplished in 69% yield by enolization (TBSOTf, DIPEA, -78 °C),\textsuperscript{15} regioselective epoxidation (1.1 equiv MCPBA, CH\textsubscript{3}Cl\textsubscript{2}, NaHCO\textsubscript{3}, -20 °C) and aqueous hydrolysis (Scheme 4).\textsuperscript{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: [\alpha]_D +24.0; natural hortonone A: [\alpha]_D +24.0; synthetic hortonone B: [\alpha]_D -37.5; natural hortonone B: [\alpha]_D -37.5).

\begin{figure}[h]
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\includegraphics[width=\textwidth]{scheme4.png}
\caption{Scheme 4. Preparation of hortonones A and B. Reagents and conditions: (a) MeLi, THF, -78 °C; (b) PCC, 4Å sieves, CH\textsubscript{3}Cl\textsubscript{2}, 1.5 h, rt; (c) TBSOTf, disopropylethylamine, CH\textsubscript{3}Cl\textsubscript{2}, -78 °C, 1h; (d) MCPBA, CH\textsubscript{3}Cl\textsubscript{2}, NaHCO\textsubscript{3}, -20 °C, 1h, aq. Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3}.}
\end{figure}

\begin{figure}[h]
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\includegraphics[width=\textwidth]{structures.png}
\caption{Figure 3. Proposed structures of natural hortonones A-C.}
\end{figure}
Conclusions
The synthesis presented here allows the preparation of all three hortones in 12-15 steps from the readily available Inhoffen-Lythgoe diol. This study has revealed that the absolute configuration of the hortones 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 (+)-hortones A-C from an alternate starting material is currently being investigated and our findings will be reported in due course.

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Notes and references
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