Published in final edited form as:

Org Biomol Chem. 2016 September 21; 14(37): 8728–8731. doi:10.1039/c6ob01738j.

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

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Abstract

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.

TOC image

Synthesis of (–)-hortonones A-C from Vitamin D₂ reveals that the natural products are of opposite absolute configuration to originally proposed.

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

[†]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

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).

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

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.

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 ($\text{CH}_3\text{MgBr}/\text{CuI}^{12}$; $\text{Me}_2\text{CuLi}/\text{TMSCl}^{13}$) 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_2Cl_2).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, CH_2Cl_2 , NaHCO_3 , −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: $[\alpha]_D -31.7$; natural hortonone A: $[\alpha]_D +24.0$; synthetic hortonone B: $[\alpha]_D -37.5$; natural hortonone B: $[\alpha]_D +24.0$).

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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.

Notes and references

1. Carr G, Williams DE, Ratnayake R, Bandara R, Wijesundara S, Tarling T, Balgi AD, Toberge M, Andersen RJ, Karunaratne V. *J Nat Prod*. 2012; 75:1189. [PubMed: 22626446]
2. (a) DeBerardinis AM, Lemieux S, Hadden MK. *Bioorg Med Chem Lett*. 2013; 23:5367. [PubMed: 23972439] (b) Meyer D, Rentsch L, Marti R. *RSC Advances*. 2014; 4:32327. (c) Banerjee U, DeBerardinis AM, Hadden MK. *Bioorg Med Chem*. 2015; 23:548. [PubMed: 25549899]
3. Lamblin M, Dabbas D, Spingarn R, Mendoza-Sanchez R, Wang T, An B, Huang DC, Kremer R, White JH, Gleason JL. *Bioorg Med Chem*. 2010; 18:4119. [PubMed: 20452225]
4. VanRheenen V, Kelly RC, Cha DY. *Tetrahedron Lett*. 1976; 17:1973.
5. Dess DB, Martin JC. *J Org Chem*. 1983; 48:4155.

6. Peterson PE, Breedlove Leffew RL, Jensen BL. *J Org Chem.* 1986; 51:1948.
7. Ito Y, Fujii S, Nakatsuka M, Kawamoto F, Saegusa T. *Org Syn.* 1980; 59:113.
8. (a) Kreuzer T, Metz P. *Eur J Org Chem.* 2008; 3:572.(b) Uyehara T, Kabasawa Y, Kato T, Furuta T. *Tetrahedron Lett.* 1985; 26:2343.
9. Ito Y, Hirao T, Saegusa T. *J Org Chem.* 1978; 43:1011.
10. (a) Wharton PS, Bohlen DH. *J Org Chem.* 1961; 26:3615.(b) Liu H-J, Wynn H. *Can J Chem.* 1986; 64:658.
11. (a) Gonzalez-Avion XC, Mourino A, Rochel N, Moras D. *J Med Chem.* 2006; 49:1509. [PubMed: 16509569] (b) Yasuda A, Yamamoto H, Nozaki H. *Bull Chem Soc Jpn.* 1979; 52:1757.(c) Yasuda A, Yamamoto H, Nozaki H. *Tetrahedron Lett.* 1976; 49:2621.
12. Dambrin V, Villieras M, Janvier P, Toupet L, Amri H, Lebreton J, Villieras J. *Tetrahedron.* 2001; 57:2155.
13. Asao N, Lee S, Yamamoto Y. *Tetrahedron Lett.* 2003; 44:4265.
14. For a recent review of 1,3-oxidative transpositions, see:Luzzio FA. *Tetrahedron.* 2012; 68:5323.
15. Yoshimura F, Sasaki M, Hattori I, Komatsu K, Sakai M, Tanino K, Miyashita M. *Chem Eur J.* 2009; 15:6626. [PubMed: 19479925]
16. Zeng C, Zhao J, Zhao G. *Tetrahedron.* 2015; 71:64.
17. (a) Atkins GM, Burgess EM. *J Am Chem Soc.* 1968; 90:4744.(b) Burgess EM, Renton HR, Taylor EA. *J Org Chem.* 1973; 38:26.
18. Brandes E, Grieco PA, Garner P. *J Chem Soc, Chem Commun.* 1988; 7:500.
19. (a) Buchi G, Vederas JC. *J Am Chem Soc.* 1972; 94:9129.(b) Schulte-Elte KH, Muller BL, Ohloff G. *Helv Chim Acta.* 1973; 56:309.
20. (a) Fehr C, Guntern O. *Helv Chim Acta.* 1992; 75:1023.(b) Fehr C, Galindo J, Guntern O. *Tetrahedron Lett.* 1990; 28:4021.(c) Serra S, Fuganti C. *Tetrahedron Asymm.* 2006; 17:1573.
21. Morris DG. *Chem Soc Rev.* 1982; 11:397.
22. (a) Sarandeses LA, Mourino A, Luche JL. *J Chem Soc, Chem Commun.* 1981:818.(b) Liotta D, Zima G. *J Org Chem.* 1980; 45:2551.

Figure 1.
Hortonones A-C

Figure 2.
Retrosynthetic analysis of hortonones A-C.

Figure 3.
Proposed structures of natural hortonones A-C.

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.

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.

Scheme 3.

Preparation of hortonone C. *Reagents and conditions:* (a) DIBAH, CH₂Cl₂, -78 °C; (b) MCPBA, CH₂Cl₂, NaHCO₃, 2h, rt; (c) MsCl, Et₃N, CH₂Cl₂, rt, 1h; (d) Na⁰, naphthalene, THF, -10 °C, 30 min; (e) Dess-Martin periodinane, CH₂Cl₂, 1h, rt.

Scheme 4.

Preparation of hortonones A and B. *Reagents and conditions:* (a) MeLi, THF, -78 °C; (b) PCC, 4Å sieves, CH₂Cl₂, 1.5 h, rt; (c) TBSOTf, diisopropylethylamine, CH₂Cl₂, -78 °C, 1h; (d) MCPBA, CH₂Cl₂, NaHCO₃, -20 °C, 1h; aq. Na₂S₂O₃.