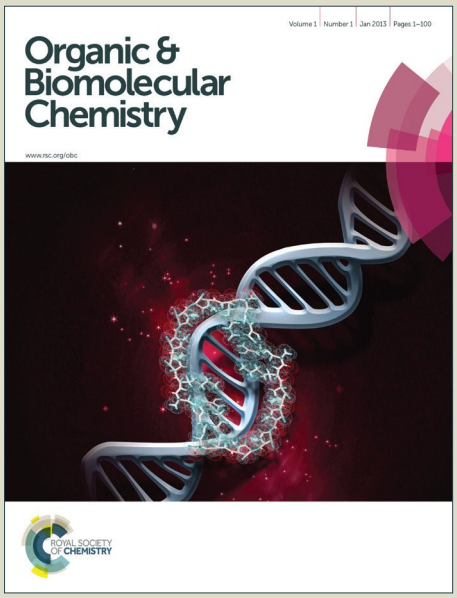
CrossMark
click for updates

View Article Online
View Journal

Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: H. Stambulyan and T. Minehan, *Org. Biomol. Chem.*, 2016, DOI: 10.1039/C6OB01738J.



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

View Article Online
DOI: 10.1039/C6OB01738J

Organic and Biomolecular Chemistry

ARTICLE

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

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Hovsep Stambulyan[a] and Thomas G. Minehan[a*]

A synthesis of hortonones A-C has been accomplished from Vitamin D_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_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*.[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.

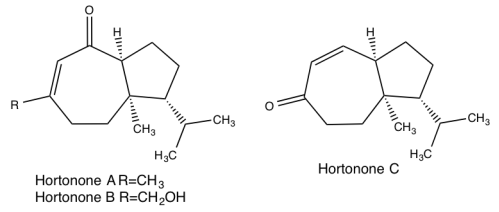


Figure 1. Hortonones A-C

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 D_2) by exhaustive oxidative cleavage[3] 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).

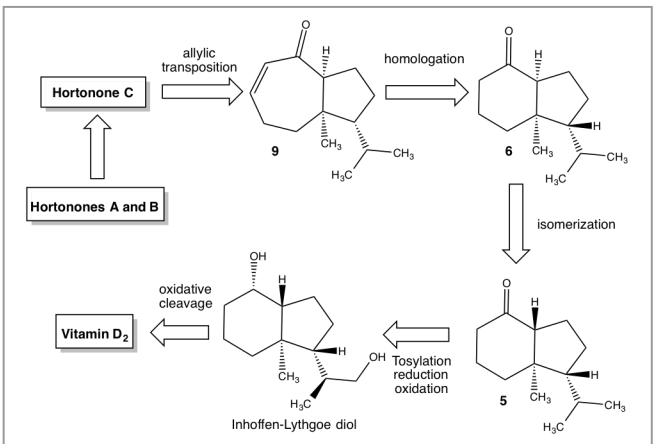


Figure 2. Retrosynthetic analysis of hortonones A-C.

[a] *Department of Chemistry and Biochemistry, California State University, Northridge, 18111 Nordhoff Street, Northridge, CA 91330*

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

Published on 22 August 2016. Downloaded by California State University at Northridge on 23/08/2016 21:45:52.

Organic & Biomolecular Chemistry Accepted Manuscript

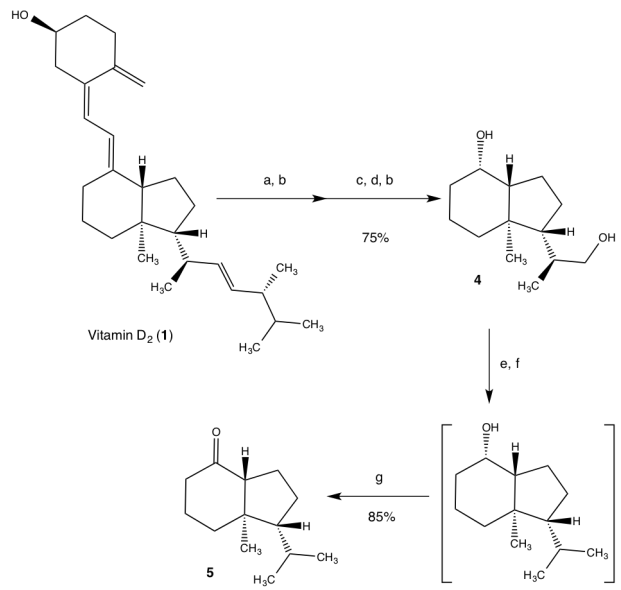
Please do not adjust margins

View Article Online
DOI: 10.1039/C6OB01778J

Published on 22 August 2016. Downloaded by California State University at Northridge on 23/08/2016 21:45:52.

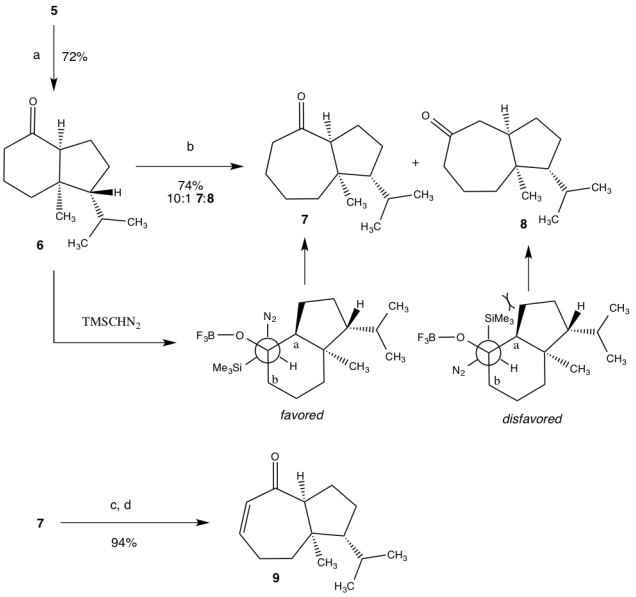
Results and Discussion

Oxidative cleavage of ergocalciferol with ozone (1:1 CH_2Cl_2/CH_3OH) followed by reductive workup with $NaBH_4$ 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 % OsO_4, NMO, acetone/H_2O),[4] oxidative cleavage (KIO_4, dioxane/H_2O) 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.[5]



Scheme 1. Synthesis of intermediate **5**. *Reagents and conditions:* (a) O_3, CH_2Cl_2, MeOH, -78 °C; (b) $NaBH_4$, MeOH, rt, 20 min; (c) 1 mol% OsO_4, NMO, acetone, H_2O, rt, 5h; (d) KIO_4, 1:1 dioxane/H_2O, rt, 3h; (e) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 1h; (f) $LiAlH_4$, THF, rt, 5h; (g) Dess-Martin Periodinane, CH_2Cl_2, 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 $FeCl_3$ were unfruitful.[7] Furthermore, reduction of the ketone to the corresponding alcohol and attempted elimination of the alcohol with Burgess reagent[17] led to an inseparable mixture of alkene regioisomers. However, it was discovered that exposure of **6** to $TMSCHN_2$ and $BF_3\bullet OEt_2$ 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**).[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_3N, CH_2Cl_2, 0° C, 2h; 50 mol % $Pd(OAc)_2$, CH_3CN, 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) $TMSCHN_2$, $BF_3\bullet OEt_2$, CH_2Cl_2, -40 °C – rt; (c) TBSOTf, Et_3N, CH_2Cl_2, rt, 2h; (d) 50 mol% $Pd(OAc)_2$, CH_3CN, rt, 12h.

Organic & Biomolecular Chemistry Accepted Manuscript

 This journal is © The Royal Society of Chemistry 20xx

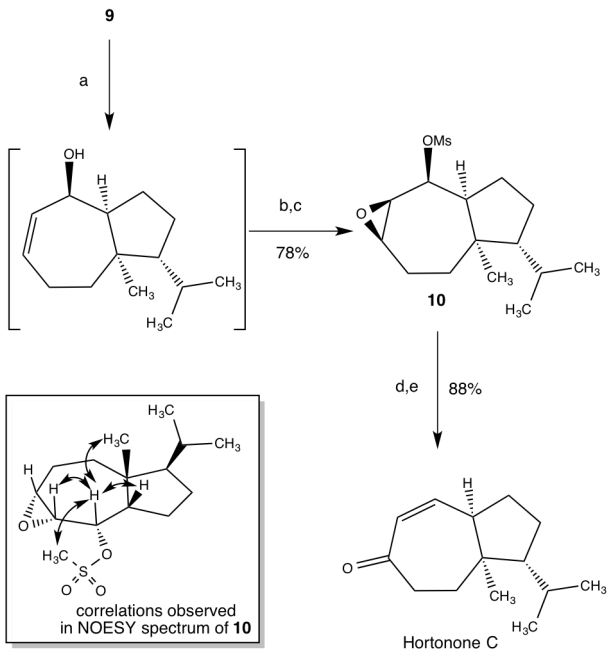
Please do not adjust margins

View Article Online
DOI: 10.1039/C6OB01738J

Published on 22 August 2016. Downloaded by California State University at Northridge on 23/08/2016 21:45:52.

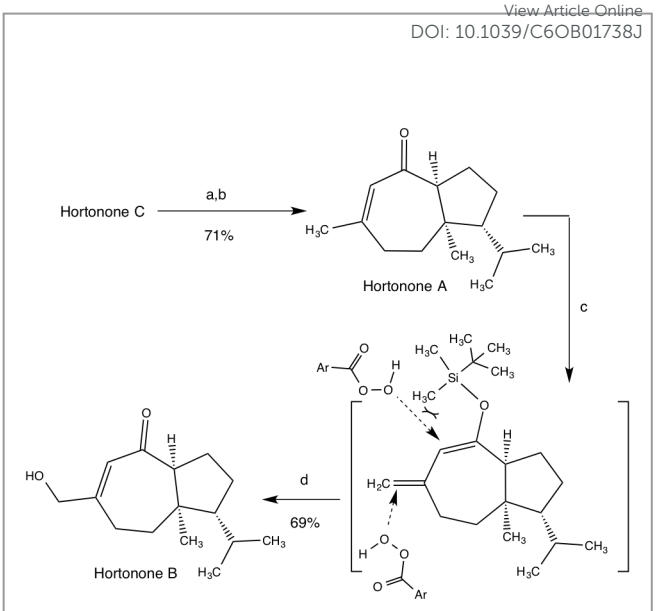
Organic & Biomolecular Chemistry Accepted Manuscript

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 reagent[5] to provide hortonone C in 88% yield. Spectroscopic data (^{1}H NMR, ^{13}C 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).



Scheme 3. Preparation of hortonone C. *Reagents and conditions:* (a) DIBAH, CH_2Cl_2, -78 °C; (b) MCPBA, CH_2Cl_2, $NaHCO_3$, 2h, rt; (c) MsCl, Et_3N, CH_2Cl_2, rt, 1h; (d) Na^0, naphthalene, THF, -10 °C, 30 min; (e) Dess-Martin periodinane, CH_2Cl_2, 1h, rt.

Initial attempts to prepare hortonone A by conjugate addition of organocuprates (CH_3MgBr/CuI[12]; Me_2CuLi/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



Scheme 4. Preparation of hortonones A and B. *Reagents and conditions:* (a) MeLi, THF, -78 °C; (b) PCC, 4Å sieves, CH_2Cl_2, 1.5 h, rt; (c) TBSOTf, diisopropylethylamine, CH_2Cl_2, -78 °C, 1h; (d) MCPBA, CH_2Cl_2, $NaHCO_3$, -20 °C, 1h; aq. $Na_2S_2O_3$.

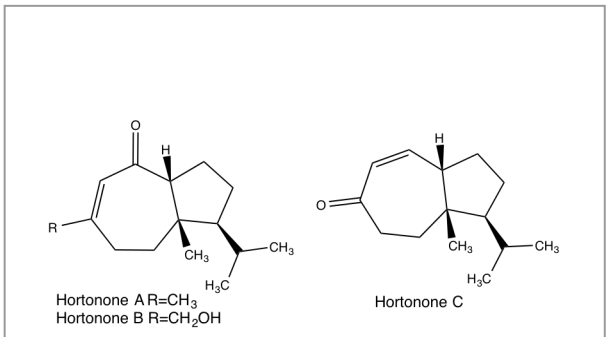


Figure 3. Proposed structures of natural hortonones A-C**.**

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 spectrocopic 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).

Please do not adjust margins

View Article Online
DOI: 10.1039/C6OB01750D

Published on 22 August 2016. Downloaded by California State University at Northridge on 23/08/2016 21:45:52.

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 at 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.

Notes and references

1 G. Carr, D. E. Williams, R. Ratnayake, R. Bandara, S. Wijesundara, T. Tarling, A. D. Balgi, M. Toberge, R. J. Andersen and V. Karunaratne *J. Nat. Prod.* 2012, **75**, 1189.
2 (a) A. M. DeBerardinis, S. Lemieux and M. K. Hadden *Bioorg. Med. Chem. Lett.* 2013, **23**, 5367; (b) D. Meyer, L. Rentsch and R. Marti, *RSC Advances* 2014, **4**, 32327; (c) U. Banerjee, A. M. DeBerardinis and M. K. Hadden *Bioorg. Med. Chem.* 2015, **23**, 548.
3 M. Lamblin, D. Dabbas, R. Spingarn, R. Mendoza-Sanchez, T. Wang, B. An, D. C. Huang, R. Kremer, J. H. White and J. L. Gleason *Bioorg. Med. Chem.* 2010, **18**, 4119.
4 V. VanRheenen, R. C. Kelly and D. Y. Cha *Tetrahedron Lett.* 1976, **17**, 1973.
5 D. B. Dess and J. C. Martin *J. Org. Chem.* 1983, **48**, 4155.
6 P.E. Peterson, R. L. Breedlove Leffew and B. L. Jensen *J. Org. Chem.* 1986, **51**, 1948.
7 Y. Ito, S. Fujii, M. Nakatsuka, F. Kawamoto and T. Saegusa *Org Syn*, 1980, **59**, 113.
8 (a) T. Kreuzer and P. Metz *Eur. J. Org. Chem.* 2008, **3**, 572; (b) T. Uyehara, Y. Kabasawa, T. Kato and T. Furuta *Tetrahedron Lett.* 1985, **26**, 2343.
9 Y. Ito, T. Hirao and T. Saegusa *J. Org. Chem.* 1978, **43**, 1011.
10 (a) P. S. Wharton and D. H. Bohlen *J. Org. Chem.* 1961, **26**, 3615; (b) H. –J. Liu and H. Wynn *Can J. Chem.* 1986, **64**, 658.
11 (a) X. C. Gonzalez-Avion, A. Mourino, N. Rochel and D. Moras *J. Med. Chem.* 2006, **49**, 1509. (b) A. Yasuda, H. Yamamoto and H. Nozaki *Bull. Chem. Soc. Jpn.* 1979, **52**, 1757. (c) A. Yasuda, H. Yamamoto and H. Nozaki *Tetrahedron Lett.* 1976, **49**, 2621.
12 V. Dambrin, M. Villieras, P. Janvier, L. Toupet, H. Amri, J. Lebreton and J. Villieras *Tetrahedron* 2001, **57**, 2155.
13 N. Asao, S. Lee and Y. Yamamoto *Tetrahedron Lett.* 2003, **44**, 4265.
14 For a recent review of 1,3-oxidative transpositions, see: F. A. Luzzio *Tetrahedron* 2012, **68**, 5323.
15 F. Yoshimura, M. Sasaki, I. Hattori, K. Komatsu, M. Sakai, K. Tanino and M. Miyashita *Chem. Eur. J.* 2009, **15**, 6626.
16 C. Zeng, J. Zhao and G. Zhao *Tetrahedron* 2015, **71**, 64.
17 (a) G. M. Atkins and E. M. Burgess *J. Am. Chem. Soc.* 1968, **90**, 4744; (b) E. M. Burgess, H. R. Renton and E. A. Taylor *J. Org. Chem.* 1973, **38**, 26.
18 E. Brandes, P. A. Grieco and P. Garner *J. Chem. Soc., Chem Commun.* 1988, **7**, 500.
19 (a) G. Buchi and J. C. Vederas *J. Am. Chem. Soc.* 1972, **94**, 9129. (b) K.H. Schulte-Elte, B. L. Muller and G. Ohloff *Helv. Chim. Acta* 1973, **56**, 309.
20 (a) C. Fehr and O. Guntern *Helv. Chim. Acta* **1992**, *75*, 1023. (b) C. Fehr, J. Galindo and O. Guntern *Tetrahedron Lett.* 1990, **28**, 4021. (c) S. Serra and C. Fuganti *Tetrahedron Asymm.* 2006, **17**, 1573.
21 D. G. Morris *Chem. Soc. Rev.* 1982, **11**, 397.
22 (a) L. A. Sarandeses, A. Mourino and J.-L. Luche *J. Chem. Soc., Chem. Commun.* 1981, 818. (b) D. Liotta and G. Zima *J. Org. Chem.* 1980, **45**, 2551.

Organic & Biomolecular Chemistry Accepted Manuscript

 This journal is © The Royal Society of Chemistry 20xx

Please do not adjust margins