Studies towards the synthesis of halomon: asymmetric hexafunctionalisation of myrcene†

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A novel dihydroxylation–dibromination–dihydroxylation sequence employing in situ protection of diols as boronate esters during the dihydroxylation reactions provides the first enantiomerically pure hexafunctionalised myrcene derivative. This concise four-step asymmetric sequence provides an advanced intermediate for the targeted synthesis of halomon via stereospecific transformations, where both stereogenic centres of the natural product have been set.

Halomon 1 is an acyclic pentahalogenated terpene isolated in pure form as a major component of the organic extracts of red algae Portieria hornemannii and characterised by X-ray crystallography by Boyd in 1992. Halomon’s biological profile – initially found to display highly differential cytotoxicity against a diverse panel of human tumor cell lines, and also shown more recently to be an inhibitor of DNA methyl transferase 1 – has attracted much interest, but there is a lack of a reliable natural source from the algae due to site-to-site and temporal variations in terpene content. Synthetic efforts have resulted in the successful synthesis of halomon, but only in racemic form and as a mixture of stereoisomers, thereby requiring subsequent separation. Nevertheless, there is a clear need for an asymmetric and stereo-selective strategy to access halomon and its related congeners for the synthesis of enantiopure halomon starting from myrcene in this fashion.

On the other hand, we and Denmark have shown that enantiomerically pure bromonium ions can be generated from enantiopure bromohydrins and/or their O-derivatives. In particular, we have shown that either regioisomer of single enantiomer 1,2-bromotosylates of terminal aliphatic alkenes can generate single enantiomer bromonium ions that can be trapped with chloride anion to give enantiopure 1,2-chlorobromides. We have also shown that Sharpless dihydroxylation of a trisubstituted olefin provides access to single enantiomer bromohydrins via stereospecific epoxide formation and bromide ring-opening, where suitable subsequent activation leads to single enantiomer bromonium ions. With these considerations in mind, we have therefore targeted dibromotetrol (3R,6S,7S)-3 as an advanced intermediate for the synthesis of enantiopure halomon starting from myrcene (Scheme 2). Here the diol of the original Δ6 trisubstituted alkenne could potentially be advanced as previously demonstrated to an enantiopure bromonium ion and trapped with chloride anion. Likewise, the bisbromohydrid tritol of the original Δ4 and C-3 methylene olefins of myrcene 2 could serve for the formation of two enantiomerically pure bromonium ions each to be trapped in a

followed by elimination of HBr and/or HCl (Scheme 1, halomon only). With halomon 1 being isolated as a single enantiomer compound this implicates the intermediacy of enantiopure bromonium ions as promoted by bromoperoxidase in the algeae.

However, despite the recent rapid advance in asymmetric olefin halogenation methods, a general method for direct enantioselective bromonium ion formation on one face of an isolated alkene followed by intermolecular regioselective and stereospecific capture with a nucleophile does not yet exist, thus precluding attempted asymmetric synthesis of halomon 1 from myrcene 2 in this fashion.

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Enantioselective bromonium ion formation

Dihydroxylation-dibromination-dihydroxylation

Scheme 2  Retrosynthesis of halomon 1 to myrcene 2 via hexafunctionalised (3R,6S,7S)-dibromotetrol 3.

Markovnikov fashion with chloride anion. Herein, we report the successful asymmetric synthesis of dibromotetrol (3R,6S,7S)-3 from myrcene 2 via a novel dihydroxylation-dibromination-dihydroxylation sequence employing in situ protection of diols as boronate esters during the dihydroxylation reactions. Critically, a citric acid buffered Upjohn reaction allows post-dibromination dihydroxylation to be effected successfully where other conditions compromise the diol dibromide products. Moreover the employment of a boronate ester as a protecting group allows quantitative and E-selective 1,4-dibromination of a diene that is otherwise impossible in the presence of a diol. To the best of our knowledge this represents the first synthesis of an enantioselectively pure hexafunctionalised myrcene derivative, and provides an advanced intermediate for the targeted synthesis of halomon 1 via subsequent stereospecific transformations.

Our studies commenced by using isoprene 4 as a model for the eastern portion of halomon, with a view to dihydroxylation known dibromide 5 into dibromodiol 6 (Table 1). However, we were aware that there have been no reports of a dihydroxylation of any kind on a 2-alkyl-1,4-dibromo-but-2-ene such as dibromide 5. Thus, isoprene was dibrominated according to the method of Alexakis19 giving the 1,4-dibromide 5 as a 94 : 6 E : Z mixture§¶ and dihydroxylation conditions were investigated (Table 1).

Table 1  Synthesis of dibromide 5 and attempted dihydroxylation to dibromodiol 6

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield 6a</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>AD-mix β + MeSO₂NH₂</td>
<td>0°</td>
</tr>
<tr>
<td>2</td>
<td>AD-mix β + MeSO₂NH₂ + NaHCO₃</td>
<td>0°</td>
</tr>
<tr>
<td>3</td>
<td>AD-mix β + MeSO₂NH₂ + NaHCO₃</td>
<td>0°</td>
</tr>
<tr>
<td>4</td>
<td>AD-mix β + MeSO₂NH₂ + PhB(OH)₂</td>
<td>0°</td>
</tr>
<tr>
<td>5</td>
<td>K₂OsO₂(OH)₄, NMO</td>
<td>0°</td>
</tr>
<tr>
<td>6</td>
<td>K₂OsO₂(OH)₄, NMO, PhB(OH)₂</td>
<td>0°</td>
</tr>
<tr>
<td>7</td>
<td>K₂OsO₂(OH)₄, NMO, citric acid</td>
<td>77</td>
</tr>
</tbody>
</table>

a  Isolated yield after chromatography. b  Dihydroxylation were performed with 0.5 mol% K₂OsO₂(OH)₄, 1 mol% (DHQD)₂PHAL, K₂Fe(CN)₆ (3 equiv.), K₂CO₃ (3 equiv.) and MeSO₂NH₂ in BuOH–H₂O. § Characteristic signals for epoxides could be seen in the ¹H NMR of the crude reaction mixtures. ¶ An additional 1.5 mol% of K₂OsO₂(OH)₄ and 3 mol% (DHQD)₂PHAL were added, and a 3 : 2 ratio of K₂CO₃ : NaHCO₃ was employed. †† The expected boronate ester was not observed. b  Acetone : water (9 : 1) as solvent. h  CH₂Cl₂ as solvent. i  No reaction of 5 was observed. j  BuOH : H₂O (1 : 1) as solvent.

Having demonstrated an effective dibromination–dihydroxylation on isoprene, attention turned to myrcene 2 where we wished to effect a dihydroxylation–dibromination–dihydroxylation sequence (cf. Scheme 2). A regioselective Sharpless dihydroxylation for the trisubstituted olefin of myrcene has been reported,26 but information on the sense of induction or enantiomeric excess was not provided. In the event, asymmetric dihydroxylation of myrcene 2 gave diol (3R)-77 as expected§§ in 91% ee §§ (Scheme 3). Attempted dibromination of diene diol 7 to give dibromide 8 failed – as expected – due to presumed competing intramolecular bromoetherification pathways.¶¶ Instead, myrcene 2 was dihydroxylated with super AD-mix β28 and added phenyl boronic acid22 to give boronate ester 9 directly, also in 91% ee, as revealed by H₂O₂-mediated boronate deprotection24 to diole 7 §§. Here, not only does the addition of phenylboronic acid allow for the in situ protection of the newly installed 1,2-diol functionality, we also considered that the boronate ester would function as a uniquely effective protecting group in the subsequent bromination, where such diols otherwise protected in an additional synthetic step as e.g., benzylidenes or as alkyl acetics may retain sufficient nucleophilicity to participate in otherwise competing intramolecular bromoetherifications reactions.29

Much to our delight, E-selective 1,4-dibromination of the diene 9 proceeded smoothly with molecular bromine without interference from the protected alcohol groups to give dibromide 10 in quantitative yield. || The application of the citric acid buffered Upjohn reaction25 (cf. dibromide 5 to diole 6, Table 1, entry 7) to dibromide 10 did not provide diol 11, but instead a moderate yield (45%) of inseparable bisboronates 12 and 13 was obtained. Here, under the conditions of reaction, evidently dihydroxylation is proceeding, but the isolation of the bisboronates implicates intramolecular boronate ester exchanges.
The crystal structure of (3R,6S,7S)-3

Accordingly, citric acid buffered Upjohn dihydroxylation of 10 with added phenylboronic acid – a further novel variation on the Upjohn reaction – gave diastereomeric bisboronates 12 and 13 as an approximate 1:1 mixture of diastereoisomers in 85% yield.†† However, in contrast to the facile deprotection of boronate 9 with hydrogen peroxide, attempted global deprotection of the bisboronate mix 12 and 13 under the same conditions led only to low and variable mass recoveries (0–35% yield) of the two expected diastereomeric tetrabromides (3R,6R,7R)-3 and (3R,6S,7S)-3.*** Deprotection instead using modified conditions of Padwa,10 gave the separable diastereomeric dibromotetrols (3R,6R,7R)-3 and (3R,6S,7R)-3 in 82% combined yield.††† Dibromotetrol (3R,6S,7S)-3 proved to be crystalline, and the X-ray crystal structure (Fig. 1) confirmed the original sense of induction in the Sharpless asymmetric dihydroxylation as well as all other relative and absolute configurations.

In conclusion we have demonstrated a successful asymmetric dihydroxylation–dibromination–dihydroxylation sequence employing in situ protection of diols as boronate esters during the dihydroxylation reactions to rapidly assemble the first enantiopure hexafunctionalised myrcene derivative in just four steps. This concise asymmetric sequence provides an advanced intermediate for the targeted synthesis of halomon 1 via subsequent stereospecific transformations (vide supra),14 where both stereogenic centres of the natural product have already been set. Such work is ongoing and will be reported in due course.

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Notes and references
† However, to the best of our knowledge the formation of an enantiopure bromonium ion of a 1,1-disubstituted alkene has not yet been demonstrated.
‡ This ratio is comparable with that reported in literature at 92:8 [ref. 19].
§ See ESI‡ for details.
¶ The putative epoxides proved to be volatile and only traces of material could be isolated after attempted column chromatography.
** Small quantities of the (R*,S*)-diol was also obtained (see ESI††). This arises from syn-dihydroxylation of the minor Z-isomer 5.
†† The reaction mixture under these acidic conditions was characteristically green in colour that faded as the reaction proceeded. See ref. 25 for the significance of this colour.
†‡ The absolute configuration was assigned on the basis of the Sharpless mmemonic (ref. 16).
§§ The ee was calculated as 91% by comparison of the measured rotation with the reported rotation for (3R)-7 (ref. 27) (see ESI†††).
¶¶ Complex product mixtures were obtained.
††† As a 96:4 E:Z mixture.
*** H2O2 deprotection studies with the phenyl boronate ester of dibromotetrol 6 (not shown) showed characteristic signals for epoxides in the 1H NMR of the crude reaction mixtures. We invoke epoxide formation in the attempted H2O2 deprotection of boronates 12 and 13 also, and subsequent decomposition in the work-up and/or purification process (chromatography).
‡‡‡ The dibromotetrols were obtained as a ca. 1:1 mixture, and analytically pure samples of each could be obtained by careful column chromatography (see ESI†).

7 The racemic synthesis of two naturally occurring halogenated monoterpenes of the halomon class have been reported: M. E. Jung and M. H. Parker, J. Org. Chem., 1997, 62, 7094–7095.
9 Hira and coworkers (ref. 6) employed a stepwise bromochlorination of myrcene to obtain 2,6-dibromo-3-(bromomethyl)-1,3,7-trichloro-7-methyloctane as a mixture of four diastereoisomers.
However, all attempts to effect an elimination of HBr to yield halomonone were reported as unsuccessful.


A Sharpless asymmetric dihydroxylation of a 1,6-dibromohexa-2,4-diene under modified conditions has been reported: O. Hidestål, R. Ding, A. Almesäker and U. M. Lindström, Green Chem., 2005, 7, 259–261.


