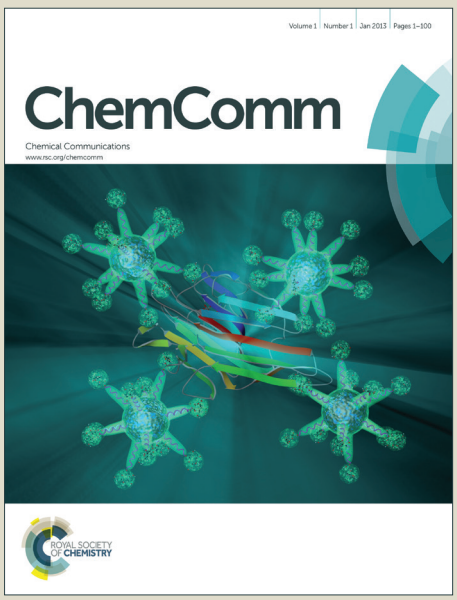
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

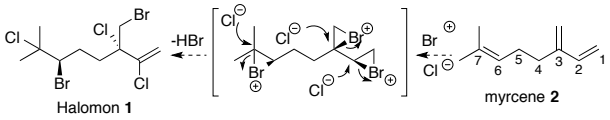
Studies Towards the Synthesis of Halomon: Asymmetric Hexafunctionalisation of Myrcene†

D. Christopher Braddock,* Alison X. Gao, Andrew J. P. White and Mariko Whyte

Receipt/Acceptance Data **[DO NOT ALTER/DELETE THIS TEXT]**
Publication data **[DO NOT ALTER/DELETE THIS TEXT]**
DOI: 10.1039/b000000x [DO NOT ALTER/DELETE THIS TEXT]

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.

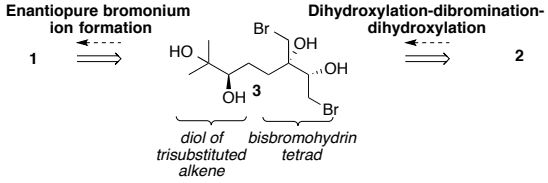
Halomon **1** is an acyclic pentahalogenated terpene isolated in pure form as a major component of the organic extracts of red algae *Portieria hornemannii* and characterised by X-ray crystallography by Boyd in 1992.[1] Halomon's biological profile – initially found to display highly differential cytotoxicity against a diverse panel of human tumor cell lines,[1] and also shown more recently to be an inhibitor of DNA methyl transferase 1[2] – has attracted much interest,[3] but there is a lack of a reliable natural source from the algae due to site-to-site and temporal variations in terpene content.[4] 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.[5,6] There is therefore a clear need for an asymmetric and stereoselective strategy to access halomon and its related congeners[4,7] for further biological evaluation. However, the introduction of each of the five halogens via site-selective functionalisations, including asymmetric fashioning of the two halogen-bearing stereocentres and installation of the vinyl chloride offers significant synthetic challenge.



Scheme 1. Halomon **1** and its proposed biogenesis from myrcene **2**.

Halomon **1** and its related congeners are considered to arise biogenetically via enzyme mediated Markovnikov addition of BrCl to the Δ^1, Δ^6 and/or C-3 methylene double bonds of myrcene **2** followed by elimination of HBr and/or HCl (Scheme 1, halomon only).[8,9,10] With halomon **1** being isolated as a single enantiomer compound this implicates the intermediacy of enantiopure bromonium ions as promoted by bromoperoxidase in the algae.[11] However, despite the recent rapid advance in asymmetric olefin halogenation methods,[12] 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,[13] thus precluding attempted asymmetric synthesis of halomon **1** from myrcene **2** in this fashion.

On the other hand, we[14] and Denmark[15] 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.[14a] We have also shown that Sharpless dihydroxylation[16] of a trisubstituted olefin provides access to single enantiomer bromohydrins via stereospecific epoxide formation[17] and bromide ring-opening,[18] where suitable subsequent activation leads to single enantiomer bromonium ions.[14b,c] With these considerations in mind, we have therefore targeted dibromotetrol (3*R*,6*S*,7*S*)-**3** as an advanced intermediate for the synthesis of enantiopure halomon starting from myrcene **2** (Scheme 2). Here the diol of the original Δ^6 trisubstituted alkene could potentially be advanced as previously demonstrated to an enantiopure bromonium ion and trapped with chloride anion. Likewise, the bisbromohydrin tetrad of the original Δ^1 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 Markovnikov fashion with chloride anion. Herein, we report the successful asymmetric synthesis of dibromotetrol (3*R*,6*S*,7*S*)-**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 enantiomerically pure hexafunctionalised myrcene derivative, and provides an advanced intermediate for the targeted synthesis of halomon **1** via subsequent stereospecific transformations.



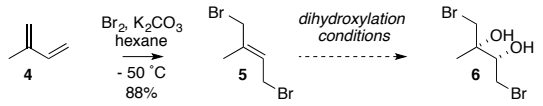
† Electronic Supplementary Information (ESI) available: Experimental procedures, characterising data and copies of ^{1}H and ^{13}C NMR spectra for compounds **5-7**, **9-10**, **12/13** mix, (3*R*,6*S*,7*S*)-**3** and (3*R*,6*R*,7*R*)-**3**; X-ray crystallographic details for **6** and (3*R*,6*S*,7*S*)-**3**.

* c.braddock@imperial.ac.uk

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

Our studies commenced by using isoprene **4** as a model for the eastern portion of halomon, with a view to dihydroxylating 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 Alexakis[19] 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**.

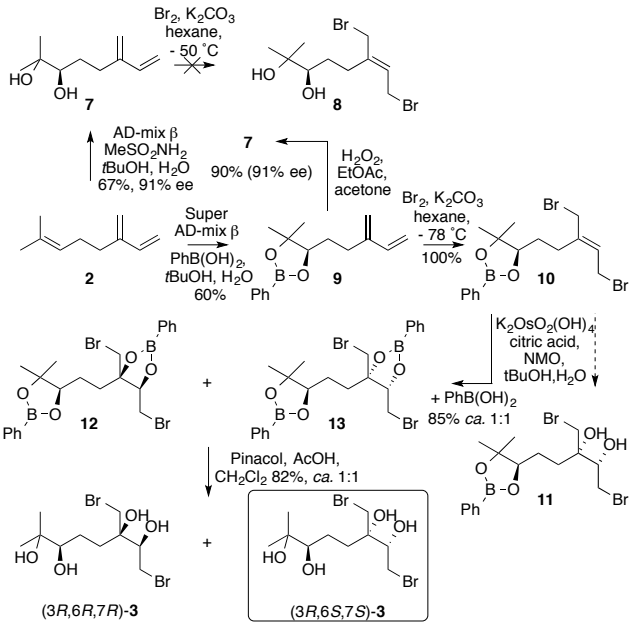


Entry	Conditions	Yield **6**[a]
1	AD-mix β + $MeSO_2NH_2$[b]	0[c]
2	AD-mix β + $MeSO_2NH_2$[b] + $NaHCO_3$	0[c]
3	AD-mix β + $MeSO_2NH_2$[b] + $NaHCO_3$[d]	0[c]
4	AD-mix β + $MeSO_2NH_2$[b] + $PhB(OH)_2$[e]	0[f]
5	$K_2OsO_2(OH)_4$, NMO[g]	0[c]
6	$K_2OsO_2(OH)_4$, NMO, $PhB(OH)_2$[h]	0[i]
7	$K_2OsO_2(OH)_4$, NMO, citric acid[j]	77

[a] Isolated yield after chromatography; [b] Dihydroxylations were performed with 0.5 mol% $K_2OsO_2(OH)_4$, 1 mol% $(DHQD)_2PHAL$, $K_3Fe(CN)_6$ (3 equiv.), K_2CO_3 (3 equiv.) and $MeSO_2NH_2$ in $^tBuOH/H_2O$; [c] Characteristic signals for epoxides could be seen in the ^1H NMR of the crude reaction mixtures; [d] An additional 1.5 mol% of $K_2OsO_2(OH)_4$ and 3 mol% $(DHQD)_2PHAL$ were added, and a 3:2 ratio of K_2CO_3:$NaHCO_3$ was employed; [e] An additional 1 mol% of $K_2OsO_2(OH)_4$ and 3 mol% $(DHQD)_2PHAL$ were added; [f] The expected boronate ester was not observed; [g] Acetone:water (8:1) as solvent; [h] CH_2Cl_2 as solvent; *i* No reaction of **5** was observed; [j] $^tBuOH:H_2O$ (1:1) as solvent.

Attempted Sharpless asymmetric dihydroxylation (entry 1) of dibromide **5** with AD-mix-β and added methanesulphonamide[16] failed, however, where the substrate was consumed but no diol **6** was detected, and characteristic signals for epoxides could be observed in the ^1H NMR spectrum of the crude material.[¥] The limited literature precedent for osmium catalysed asymmetric dihydroxylation of allylic bromides suggests that $NaHCO_3$-buffered AD-mix can suppress the unwanted pathways of hydrolysis of the starting material and base mediated ring-closure of the bromohydrin product to an epoxide.[20] However, attempts to apply these conditions to the conversion of dibromide **5** into diol **6** also failed (entry 2). The use of other reported protocols for allylic bromides (entry 3)[21] or attempted *in situ* capture of the diol as a boronate ester by addition of phenylboronic acid (entry 4)[22] also failed. The observation of characteristic epoxide signals in each of the crude reaction mixtures led us to conclude that the inherently basic nature of the reaction medium was the central problem. Attempted non-asymmetric dihydroxylations under relatively neutral Upjohn conditions (entry 5)[23] or using Narasaka's anhydrous modification of the Upjohn procedure (entry 6)[24] also failed. Gratifyingly, the application of an osmium catalysed dihydroxylation under acidic conditions – a modified Upjohn reaction with NMO as the re-oxidant with added citric acid[25] – allowed the smooth conversion of dibromide **5** into (±)-dibromodiol **6** in good isolated yield (entry 7),[††,**] and its structure was confirmed by X-ray crystallography.[¶]

Having demonstrated an effective dibromination-dihydroxylation on isoprene, attention turned to myrcene **2** where we wished to effect a dihydroxylation-dibromination-dihydroxylation sequence (*c.f.* Scheme 2). A regioselective Sharpless dihydroxylation for the trisubstituted olefin of mrycene has been reported,[26] but information on the sense of induction or enantiomeric excess was not provided. In the event, asymmetric dihydroxylation[16] of myrcene **2** gave diol (3*R*)-**7**[27] 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 β[28] and added phenyl boronic acid[22] to give boronate ester **9** directly**,** also in 91% ee, as revealed by H_2O_2-mediated boronate deprotection[24] to diol **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 acetals may retain sufficient nucleophilicity to participate in otherwise competing intramolecular bromoetherifications reactions.[29]



Scheme 3. Hexafunctionalisation of myrcene **2** via a dihydroxylation-dibromination-dihydroxylation sequence employing boronate esters as protecting groups.

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 reaction[25] (*c.f.* dibromide **5** to diol **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 intermolecular boronate ester exchanges. 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[24] led only to low and variable mass recoveries (0-35% yield) of the two expected diasteromeric tetrols (3*R*,6*R*,7*R*)-**3** and (3*R*,6*S*,7*S*)-**3**.††† Deprotection instead using modified conditions of Padwa,[30] gave the separable diastereomeric dibromotetrols (3*R*,6*S*,7*S*)-**3** and (3*R*,6*R*,7*R*)-**3** in 82% combined yield.*** Dibromotetrol (3*R*,6*S*,7*S*)-**3** proved to be crystalline, and the X-ray crystal structure (Figure 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.

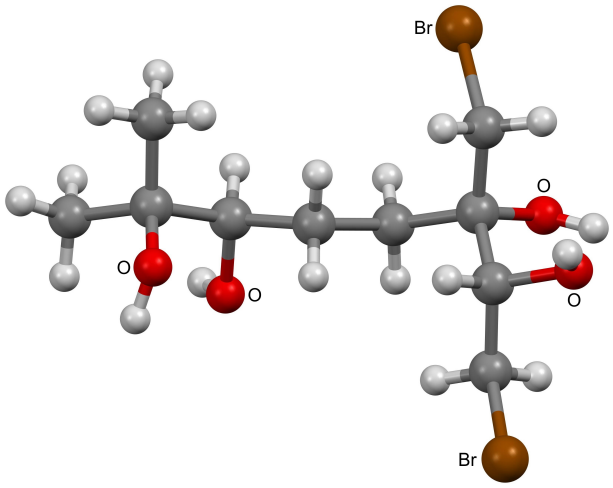


Figure 1. The crystal structure of (3*R*,6*S*,7*S*)-**3**.

We thank the Department of Chemistry, Imperial College London for support (to A. X. G. and M. W.).

D. Christopher Braddock,* Alison Gao, Andrew, J. P. White and Mariko Whyte
Department of Chemistry, Imperial College London, London, SW7 2AZ, UK. Fax: +44(0)2075945805; Tel: +44(0)2075945772; E-mail: c.braddock@imperial.ac.uk.

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 Electronic Supporting Information 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*-dibromide **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 mnemonic (ref. 16).

§§ The ee was calculated as 91% by comparison of the measured rotation with the reported rotation for (3*R*)-**7** (ref. 27) (see ESI).

¶¶ Complex product mixtures were obtained.

¥¥ As a 96:4 *E*:*Z* mixture.

††† H_2O_2 deprotection studies with the phenyl boronate ester of dibromodiol **6** (not shown) showed characteristic signals for epoxides in the ^{1}H NMR of the crude reaction mixtures. We invoke epoxide formation in the attempted H_2O_2 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).

1 Fuller, R. W.; Cardellina II, J. H.; Kato, Y.; Brinen, L. S.; Clardy, J.; Snader, K. M.; Boyd, M. R. *J. Med. Chem.* **1992**, *35*, 3007-3011.

2 Andrianasolo, E. H.; France, D.; Cornell-Kennon, S.; Gerwick, W. H. *J. Nat. Prod.* **2006**, *69*, 576-579.

3 Egorin, M. J.; Sentz, D. L.; Rosen, D. M.; Ballasteros, M. F.; Kearns, C. M.; Callery, P. S.; and Eiseman, J. L.; *Cancer Chemother. Pharmacol.* **1996**, *39*, 51-60. (b) Egorin, M. J.; Rosen, D. M.; Benjamin, S. E.; Callery, P. S.; Sentz, D. L; Eiseman, J. L. *Cancer Chemother. Pharmacol.* **1997**, *41*, 9-14.

4 Fuller, R. W.; Cardellina II, J. H.; Jurek, J.; Scheuer, P. J.; Alvarado-Lindner, B.; McGuire, M.; Gray, G. N.; Steiner, J. R.; Clardy, J.; Menez, E.; Shoemaker, R. H.; Newman, D. J.; Snader. K. M.; Boyd, M. R. *J. Med. Chem.* **1994**, *37*, 4407-4411.

5 Schlama, T.; Baati, R.; Gouverneur, V.; Valleix, A.; Falck, J. R.; Mioskowski, C. *Angew. Chem. Int. Ed.,* **1998**, *37*, 2085-2087.

6 Sotokawa, T., Noda, T., Pi, S. and Hirama, M., *Angew. Chem. Int. Ed.,* **2000**, *39*, 3430-3432.

7 The racemic synthesis of two naturally occurring halogenated monoterpenes of the halomon class have been reported: Jung, M. E.; Parker, M. H. *J. Org. Chem.* **1997**, *62*, 7094-7095.

8 Burreson, B. J.; Wooland, F. X.; Moore, R. E. *Chem. Lett.* **1975**, 1111-1114.

9 Hirama 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 halomon **1** were reported as unsuccessful.

10 Geranyl diphosphate has been proposed to be the common biogenetic precursor for the wider family of monoterpenes in macrophytic red algae: Wise, M. L.; Croteau, R. In *Comprehensive Natural Product Chemistry*; Barton, D. H. R.; Nakanishi, K.; Meth-Cohn, O. Eds.; Pergamon: Elmsford, NY, 1999; Vol. 2, pp 97-153.

11 For a review on halogenating enzymes see: Butler A.; Sandy, M. *Nature*, **2009**, 460, 848–854 and references cited therein.

12 For selected reviews see: (a) Zheng, S.; Schienebeck, C. M.; Zhang, W.; Wang, H.-Y.; Tang, W. *Asian J. Org. Chem.* **2014**, 3, 366-376; (b) Cheng, Y. A.; Yu, W. Z.; Yeung, Y.-Y. *Org. Biomol. Chem.*, **2014**, *12*, 2333-2343; (b) Murai, K.; Fujioka, H. *Heterocycles* **2013**, *87*, 763–805; (d) Denmark, S. E.; Kuester, W. E.; Burk, M. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10938–10953; (e) Hennecke, U. *Chem. Asian J.* **2012**, *7*, 456–465; (f) Tan, C. K.; Zhou, L.; Yeung, Y.-Y. *Synlett* **2011**, 1335–1339; (g) Castellanos, A.; Fletcher, S. P. *Chem. Eur. J.* **2011**, *17*, 5766–5776; (h) Chen, G.; Ma, S. *Angew. Chem., Int. Ed.* **2010**, 49, 8306–8308.

13 For a review on asymmetric intermolecular halogenation of alkenes see: Chen, J.; Zhou, L. *Synthesis* **2014**, *46*, 586-595.

14 (a) Braddock, D. C.; Hermitage, S. A.; Kwok, L.; Pouwer, R.; Redmond, J. M.; White, A. J. P. *Chem. Commun.* **2009**, 1082-1084; (b) Braddock, D. C.; Marklew, J. S.; Thomas, A. J. F. *Chem.*

Commun. **2011**, *47*, 9051-9053; (c) Braddock, D. C.; Marklew, J. S.; Foote, K. M.; White, A. J. P. *Chirality* **2013**, *25*, 692-700.
15 Denmark, S. E.; Burk M. T.; Hoover, A. J. *J. Am. Chem. Soc.* **2010**, *132*, 1232–1233 and references cited therein.
16 Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768-2271.
17 Corey, E. J.; Noe, M. C.; Shieh, W.-C. *Tetrahedron Lett.* **1993**, *34*, 5995–5998.
18 Couladouros E. A.; Vidali, V. P. *Chem.-Eur. J.* **2004**, *10*, 3822–3835.
19 Falciola, C. A.; Tissot-Crosset, K.; Reyneri, H.; Alexakis, A. *Adv. Synth. Catal.* **2008**, *350*, 1090-1100.
20 Kolb, H. C.; Bennani, Y. L.; Sharpless, K. B. *Tetrahedron: Asymm.* **1993**, *4*, 133-141.
21 A Sharpless asymmetric dihydroxylation of a 1,6-dibromohexa-2,4-diene under modified conditions has been reported: Hidestål, O.; Ding, R.; Almesåaker, A.; Lindström, U. M. *Green Chem.* **2005**, *7*, 259-261.
22 Hövelmann, C. H.; Muñiz, K. *Chem. Eur. J.* **2005**, *11*, 3951-3958.
23 VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973-1976.
24 Gypser, A.; Michel, D. Nirschl, D. S.; Sharpless, K. B. *J. Org. Chem.* **1998**, *63*, 7322-7327 and references cited therein.
25 Dupau, P.; Epple, R.; Thomas, A. A; Fokin, V. V.; Sharpless, K. B. *Adv. Synth. Catal.* **2002**, *344*, 421-433.
26 Dihydroxylation of myrcene using AD-mix α: Wu, J. Y.; Stanzl, B. N.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 13214-13216.
27 (3*R*)-**7** has been reported via an alternative route: Hioki, H.; Ooi, H.; Hamano, M.; Mimura, Y.; Yoshio, S.; Kodama, M.; Ohta, S.; Yanai, M.; Ikegami, S. *Tetrahedron* **2001**, *57*, 1235-1246.
28 For 'super' AD-mix see footnote 76 in: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem Rev.* **1994**, *94*, 2483-2547.
29 For recent representative examples of intramolecular bromoetherifications of unsaturated ethers see: (a) Braddock, D. C.; Millan, D. S.; Perez-Fuertes, Y.; Pouwer, R.; Sheppard, R. N.; Solanki, S.; White, A. J. P. *J. Org. Chem.* **2009**, *74*, 1835-1841; (b) Synder, S. A.; Brucks, A. P.; Treitler, D. S.; Moga, I. *J. Am. Chem. Soc.* **2012**, *134*, 17714-17721and references cited therein.
30 Padwa, A.; Wang, Q. *J. Org. Chem.* **2006**, *71*, 7391-7402 and reference cited therein.

GRAPHICAL ABSTRACT