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Enantiospecific bromonium ion generation and intramolecular capture: a model system for asymmetric bromonium ion-induced polyene cyclisations†

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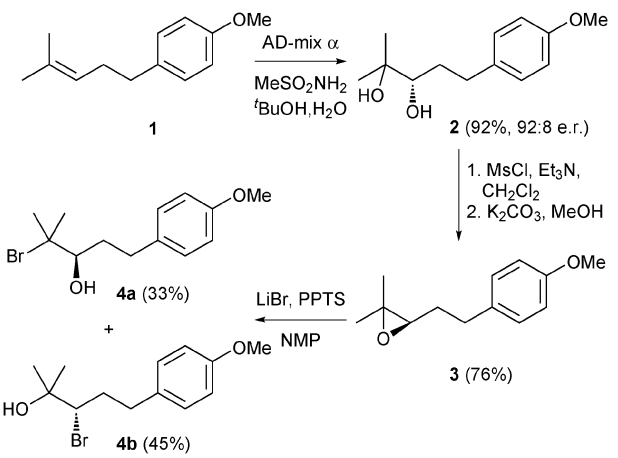
Scalemic bromonium ions generated enantiospecifically by the action of catalytic triflic acid on scalemic regioisomeric bromohydrin derivatives are trapped intramolecularly, enantiospecifically and regioselectively to give bicyclic brominated carbocycles in excellent yield and high enantiomeric excess. This enantiospecific pathway is not significantly perturbed by the addition of a trisubstituted alkene.

Biomimetic cationic polyene cyclisations of terpenes by electrophilic initiators to give polycyclic terpenoids are tremendously powerful synthetic processes.[1,2] The first direct *bromonium* ion-induced polyene cyclisation was described by Van Tamelen in 1966 as initiated by NBS,[3] but in this, and other early work,[4a–e] the cyclisations were necessarily racemic and very low yielding. Later, the use of 2,4,4,6-tetrabromocyclohexadienone (TBCO) in acetonitrile or nitromethane resulted in sufficiently efficient brominative cyclisations to give monocarbocycles and/or bicarbocycles that the total synthesis of a number of naturally occurring compounds could be accomplished.[4f–k] The recent work of Snyder[5] has shown that bromodiethylsulphonium bromopentachloroantimonate (BDSB) is an extraordinarily useful reagent for the direct bromonium-induced cyclisation of a wide range of polyenes giving mono-, bi, tri- and even tetracyclic carbocycles in high yield, but as necessarily racemic products.[6] A driving force for the development of these reactions is the continual isolation of complex polycyclic brominated natural products[7]—*as single enantiomers*—where their biogenesis are generally considered to be enzyme mediated asymmetric bromonium ion-induced polyene cyclisations,[8] and these isolations continue to date.[9] Selected cyclisations have been effected enzymatically, giving single enantiomer products.[10] However, a non-enzymatic asymmetric polyene cyclisation as induced by an enantiopure bromonium ion has yet to be reported.[11,12] We have recently reported the first generation and intermolecular trapping of enantiomerically pure bromonium ions to give enantiomerically pure bromochloride adducts.[13] In that previous work we had generated enantiopure bromonium ions by the action of thionyl chloride or titanium tetrachloride on enantiopure bromohydrin or sulphonate derivatives respectively with concomitant stereospecific NGP of the bromide. The enantiopure bromonium ions were then captured stereospecifically, and in high yield, by necessarily present chloride anion. In order to extend this methodology to the initiation of polyene cyclisations with a bromonium ion we considered that we would require (i) synthetic access to enantiopure (or enantioenriched) bromohydrins;‡ (ii) efficient activation of the bromohydrin (or derivative) to form a scalemic bromonium ion in the absence of a nucleophilic counterion; (iii) effective enantiospecific intramolecular trapping without catastrophic erosion of enantiomeric purity by rapid bromonium ion-alkene exchange (Scheme 1).[14] We also considered that this overall strategy should be high yielding since the bromonium ion



Scheme 1 Preparation of enantioenriched bromohydrins.

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† Electronic supplementary information (ESI) available: Notes ‡, §, ¶, ¥, ††, **, ‡‡, §§, ¶¶, ¥¥, †††, ***, ‡‡‡, §§§, ¶¶¶ and ¥¥¥, general experimental, experimental details and characterising data for compounds **1–3**, **4a–b**, **5a–b**, **6a–b** and **7**, ^{1}H and ^{13}C NMR spectra for compounds **1–3**, **4a–b**, **5a–b**, **6a–b** and **7** including ^{13}C NMR spectra displaying bromine isotopic shifts for **4a** and **4b**, determination of enantiomer ratios (e.r.) for **2**, **5a–b**, **6a–b** and **7** by HPLC, details for preparation of *ent*-**7** including HPLC traces for *ent*-**2** and *ent*-**7**, preliminary investigations for cyclisation of **5a** and **5b** into **7**, optimisation of anionic bromide ring-opening of epoxide **3**, procedures and data for preparation and cyclisation of *des*-bromo **4b**, and details of experiment for cyclisation of *ent*-**6a** in the presence of added alkene. See DOI: 10.1039/c1cc13619d

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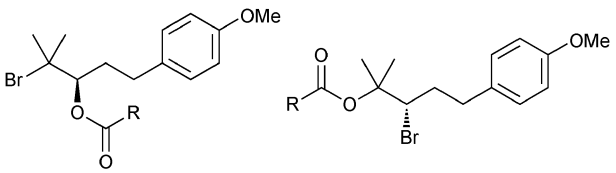
would be formed, and only formed, at the terminus of the polyene. Herein, we report on the generation of bromonium ions from scalemic bromohydrin derivatives—derived from anionic bromide ring-opening of scalemic epoxides—as a viable method for initiating cyclisation,[15,16] and demonstrate regioselective intramolecular trapping with a π-nucleophile to give bicyclic brominated carbocycles with essentially complete enantiospecificity in high yield. We also report that this process occurs *without significant erosion of enantiomeric purity in the presence of added trisubstituted alkene*.

Trisubstituted alkene **1**,[17,§] was dihydroxylated using AD-mix α[18] to give diol **2** in excellent yield and high enantiomer ratio (**2**: e.r. 92 : 8),[19,¶] and converted into epoxide **3** using the method of Corey (Scheme 1).[20] Ring-opening of epoxide **3** with anionic bromide was best achieved using the method of Couladorous and Vidali[¥] to give the separable tertiary bromide **4a** and secondary bromide **4b**. Their regioisomeric assignments were secured on the basis of a bromide induced ^{13}C isotopic shift (see ESI)[21] and their enantiomeric integrity confirmed by analysis of their derivatives (*vide infra*). Thus, the Sharpless dihydroxylation method allows access to enantioenriched bromohydrins of trisubstituted alkenes.



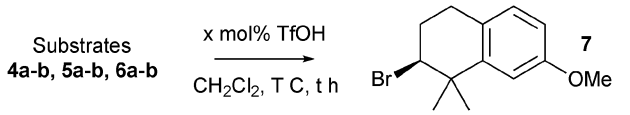
5a; R = 2,3,4,5-tetrafluorophenyl
6a; R = Me

5b; R = 2,3,4,5-tetrafluorophenyl
6b; R = Me

With scalemic bromohydrins **4a** and **4b** in hand, we considered how best to activate them. We had recently observed the spontaneous formation of a bromonium ion from a 1-bromo-2-tetrafluorobenzoate on standing,[22] and so we selected the tetrafluorobenzoate as a suitable leaving group for this study. Accordingly, tetrafluorobenzoates **5a** and **5b** were prepared from alcohols **4a** and **4b** by Steglich esterification.[23] Acetates **6a** and **6b** could also be prepared by the same method.[††] These transformations to give **5a**, **5b**, **6a** and **6b** – and evidently the preceding steps involving epoxide formation (**2** into **3**) and anionic bromide ring-opening (**3** into **4a** + **4b**) *cf*. Scheme 1 – proceeded without loss of any stereochemical integrity.[¶,**] In the event, cyclisation was effected[‡‡] by the use of catalytic triflic acid in dichloromethane (Table 1). Much to our delight, cyclisation of secondary bromobenzoate **5a** with 30 mol% TfOH in refluxing dichloromethane proceeded enantiospecifically,[¶] and essentially quantitatively, to bromocyclohexane **7**[§§] (entry 1), but where lower catalyst loading were increasingly less effective (entries 2,3).

Tertiary bromobenzoate **5b** was also efficiently cyclised under these conditions, again with essentially complete enantiospecificity, in excellent to good conversions either at reflux (entry 4) or at r.t. (entry 5). Thus tetrafluorobenzoates of *either* 2° or 3° bromohydrins derived from trisubstituted alkenes are excellent choices for the formation of scalemic bromonium ions as catalysed by triflic acid. In addition, the reaction profiles of these reactions were extremely clean. Secondary acetate **6a** was also efficiently cyclised under these conditions

Table 1 Brominative cyclisation of substrates with catalytic TfOH[a]

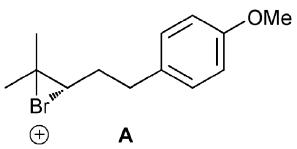


Entry	Substrate[b]	x	T/°C	t (h)	% Conversion[c]	e.r.[d]
1	**5a** (92 : 8)	30	40	3	97 (84)	91 : 9
2	**5a** (92 : 8)	10	40	16	81	nd
3	**5a** (92 : 8)	5	40	16	20	nd
4	**5b** (93 : 7)	30	40	4	94 (67)	92 : 8
5	**5b** (93 : 7)	30	r.t.	16	79	nd
6	**6a** (92 : 8)	30	40	2.5	80 (68)	84 : 16
7	**6b** (92 : 8)	30	40	2	45 (14)	nd

[a] See ESI for experimental conditions. [b] The figure in parentheses is the e.r. for this substrate. [c] As determined by inspection of the ^1H NMR spectrum after aqueous work-up. Figure in parentheses is isolated yield after column chromatography. [d] As determined by HPLC analysis by reference to a racemic sample.

but with a slight erosion in enantiomeric ratio of the product (entry 6).[¥¥] However tertiary acetate **6b** (entry 7) gave complex and varied mixtures of product and rearranged compounds.[†††] The direct cyclisation of both bromohydrins **4a** and **4b** under these conditions were also attempted, but these substrates gave complex product mixtures, from which the desired product **7** could sometimes be isolated, but where isopropylphenethylketone[17] was usually the major component.

Evidently, the transformation of **5a** (and **6a**) into **7** must necessarily proceed through bromonium ion **A***** by stereospecific NGP of the bromide—with complete inversion of configuration—on the protonated leaving group and then enantiospecific and regioselective trapping of the bromonium ion by the aromatic nucleus.[‡‡‡] The same scalemic bromonium ion **A**[§§§] can be invoked from **5b**.



A

To show the preparative utility of this method alkene **1** was dihydroxylated with AD-mix β to give *ent*-**2** (99%, 97 : 3 e.r.[¶]). Epoxide formation as before gave *ent*-**3** (53%), and anionic bromide ring-opening gave *ent*-**4a** and *ent*-**4b** (72%), which were converted—without separation—into a mixture of *ent*-**5a** and *ent*-**5b** (95%). Triflic acid catalysed cyclisation of the mixture in dichloromethane (30 mol% TfOH, 2h r.t then 2 h at reflux) gave *ent*-**7** in high yield with essentially complete enantiospecificity (84%, 96 : 4 e.r.[¶]).[¶¶¶]

In the context of developing asymmetric bromonium ion-induced polyene cyclisations it is vital to know if these enantiospecific intramolecular cyclisations onto bromonium ions will be compromised by competitive intermolecular bromonium ion transfer to alkenes[14] (alkene functionality being necessarily present in potential polyene substrates). Accordingly, triflic acid catalysed cyclisation of secondary acetate *ent*-**6a** (e.r. 96 : 4) was performed in the presence of one equivalent of 1-methylcyclohexene. Although a Friedel–Crafts alkylation adduct was formed in the reaction mixture,[¥]

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the desired bromocyclohexane *ent*-**7** was isolated in 35% yield, and with an essentially undiminished e.r. of 94 : 6.

In conclusion, we have shown that scalemic bromohydrins of trisubstituted alkenes can be readily prepared by application of the Sharpless dihydroxylation method, thereby giving access to both enantiomeric series with high enantioselectivity. Their tetrafluorobenzoate derivatives are excellent substrates for the formation of scalemic bromonium ions of a trisubstituted alkene from *either* 2° or 3° bromohydrins—or as a mixture—on treatment with catalytic quantities of triflic acid, and undergo enantiospecific regioselective cyclisation with a suitably positioned nucleophile. This enantiospecific pathway is not significantly perturbed by the addition of a trisubstituted alkene. The above findings lay the groundwork for the development of polyene cyclisations triggered by enantiomerically pure bromonium ions. Further findings will be reported in due course.

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