

Halogenated Molecules

Dihalohydration of Alkynols: A Versatile Approach to Diverse Halogenated Molecules

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Abstract: In this paper we outline how dihalohydration reactions of propargylic alcohols can be used to access a wide variety of useful halogenated building blocks. A novel procedure for dibromohydration of alkynes has been developed, and a selection of dichloro and dibromo diols and cyclic ethers were synthesized. The dihalohydration of homo-propargylic alcohols

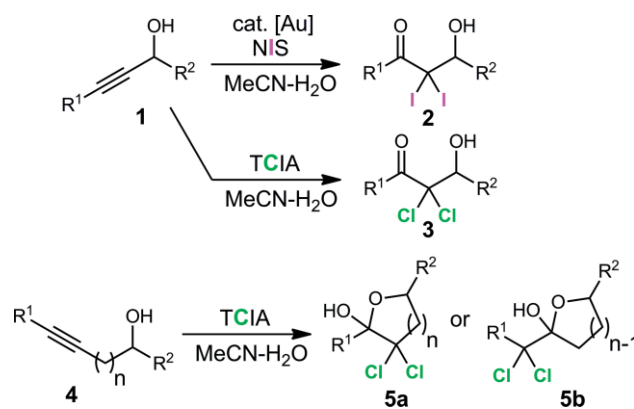
provides a useful route to 3-halofurans, which were shown to readily undergo cycloaddition reactions under mild conditions. Finally, a novel ring expansion of propargylic alcohols containing a cyclopropylalkyne provides access to halogenated alkenyl-cyclobutanes.

Introduction

Halogenated molecules play an important role in organic chemistry, both as synthetic targets themselves, and as useful reactants for a wide range of metal-catalysed reactions. For example, chlorinated and brominated functional groups are widely present in agrochemicals^[1] and in flame retardants, although the latter are causing increasing environmental concerns.^[2] They are also widely used starting materials for a range of organometallic cross-coupling methodologies.^[3] Geminal dihalides have found application as carbene or carbenoid precursors which undergo reaction with metals (e.g. Zn), metal salts (e.g. CrCl₂), or organometallic reagents (e.g. Et₂Zn) to initiate cyclopropanation or olefination reactions.^[4] Dihaloketones can also serve as useful precursors to enolates under reducing conditions.^[5] The synthesis of functionalized geminal dihalides is rare, however, as most halogenation processes require harsh conditions. For example, geminal dihalides can be generated from carbonyl groups using deoxohalogenation reagents such as PCl₅, or via halogenation of the hydrazine or oxime derivatives.^[6] Alternative methods via double carbometallation of alkynes are also incompatible with functionalized substrates.^[7] We,^[8] and others,^[9,10] have observed that dihalohydration of alkynols offers a mild and preparatively useful approach to α,α -dihaloketones. These reactions usually proceed with high regioselectivity, and provide functionalized dihaloketones from readily available precursors. To date, however, the potentially

interesting chemistry of these functionalized dihalides has not been explored in great detail.

As part of our ongoing interest in the development of novel chemistry employing propargylic alcohols,^[11] we recently reported two methods for the dihalohydration of these systems **1** (Scheme 1), with a gold-catalysed iodination reaction providing access to previously unreported α,α -diiodo- β -hydroxyketones **2**, and a catalyst-free procedure using trichloroisocyanuric acid (TCIA) giving α,α -dichloro- β -hydroxyketones **3**. The latter procedure could also be extended to alkynols **4** giving access to dichlorolactols of general structure **5a** or **5b**.



Scheme 1. Previous work on the diiodohydration and dichlorohydration of alkynols.^[8]

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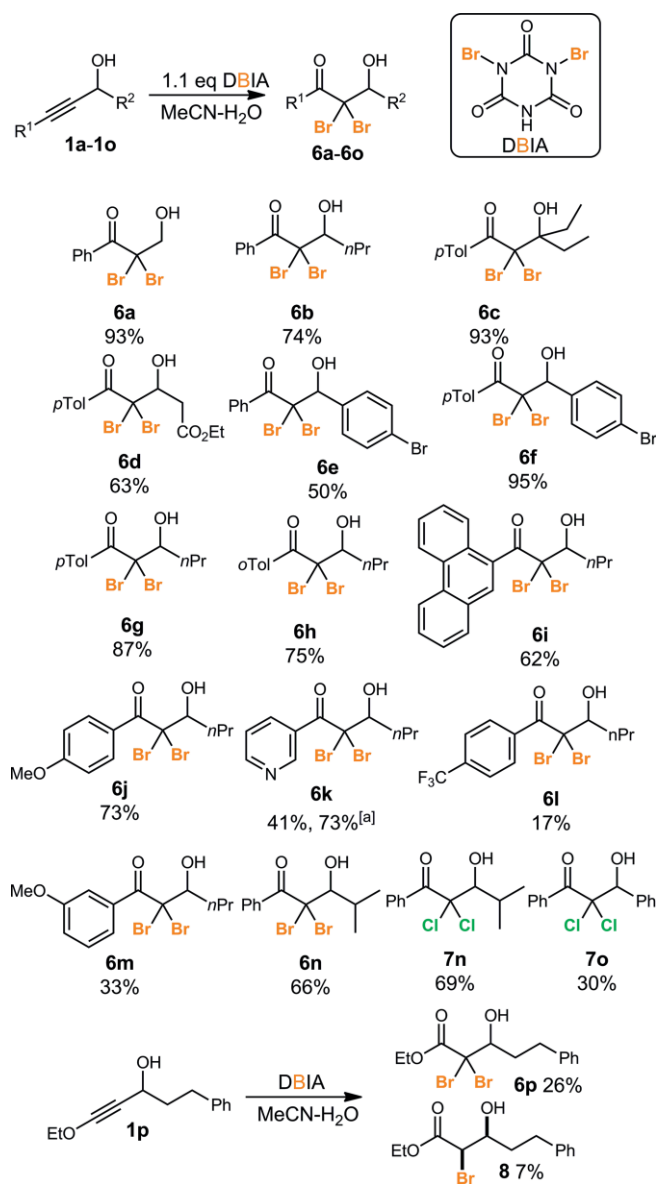
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In this article, we describe the extension of this work to the dibromohydration of alkynols, and we also describe preliminary studies on the application of geminal dibromides and dichlorides in further synthetic transformations to access a diverse range of potentially useful halogenated molecules, many of which constitute previously unreported structural frameworks.

Results and Discussion

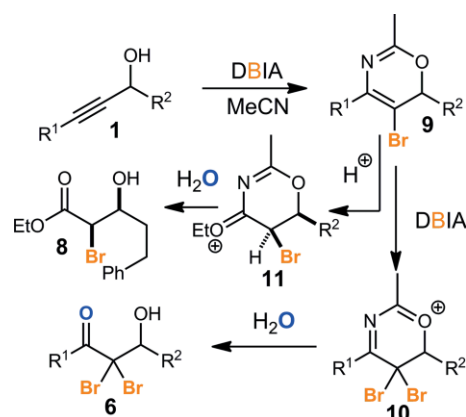
We set out to develop a method to convert readily accessible propargylic alcohols into the corresponding dibromohydroxyketones, whose properties remain relatively unexplored,^[10] although they have recently been demonstrated as effective bioisosteres for hydrated ketones in quorum-sensing inhibitors.^[12] The required dibromohydration of propargylic alcohols was achieved efficiently using dibromoisocyanuric acid (DBIA)^[13] under closely related conditions to our previously described dichlorohydration reaction.^[8] Our initial experiments suggested that the reaction was more efficient with a higher proportion of water in the reaction medium (30 % rather than 10 % H₂O in MeCN).

Pleasingly, the reaction could be applied to primary, secondary and tertiary propargylic alcohols (Scheme 2, e.g. **6a**, **6b**, **6c**). As noted previously, an aryl group on the alkyne was necessary



Scheme 2. Dibromohydration of propargylic alcohols. [a] 5 equiv. of DBIA were used.

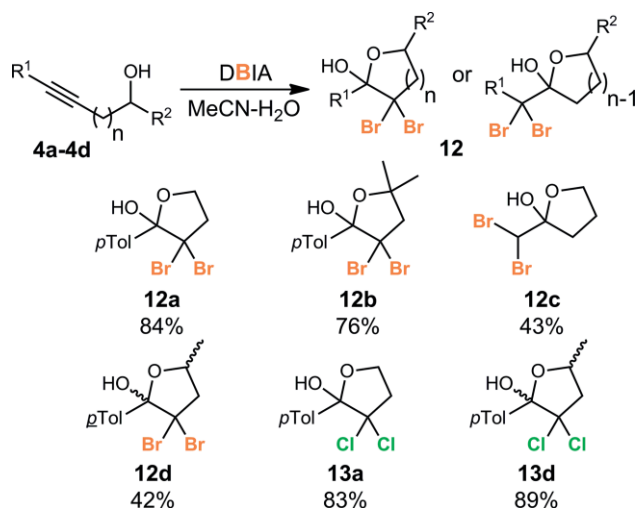
for efficient reaction. However, unsubstituted phenyl rings (**6a**, **6b**, **6e**, **6n**) and both electron rich (**6c**, **6d**, **6g**, **6h**, **6j**, **6m**) and electron deficient (**6l**, **6m**) aryl groups could be used, including examples bearing polyaromatic rings (**6i**) and a pyridine heterocycle (**6k**). A very electron-deficient benzene ring (**6l**) led to a low yield of the desired dibromide, however. Both aryl and alkyl chains could be incorporated as the R² substituent, including some functional groups (ester **6d**, aryl bromide **6e–6f**). The novel dichlorides **7n** and **7o** were also prepared using our previously reported dichlorohydration method. Interestingly, the dibromohydration of an ethoxyacetylene **1p** led to the formation of both the desired dibromide **6p** and the monobrominated compound **8**. The formation of this latter compound as a single diastereoisomer is consistent with our proposed mechanism in which the halogenation reaction proceeds via formation of heterocycle **9** through incorporation of a molecule of acetonitrile (Scheme 3). Heterocycle **9** can then undergo a second bromination to give dibromide **10** which then hydrolyses to yield the dibromoketone product **6**. Alternatively, protonation of highly electron rich heterocycle **9** (where R¹ = OEt) may take place selectively on the least hindered side to give **11** which will yield *syn*-bromohydrin **8** as the major diastereoisomer after hydrolysis.



Scheme 3. Proposed mechanism for dibromohydration.

The bromination reaction could be extended to the synthesis of dibromolactols **12a–12d** through reaction of extended alkynol derivatives (Scheme 4), including compounds containing primary (**12a**, **12c**), secondary (**12d**) and tertiary (**12b**) alcohols. Dichlorides **13a** and **13d** were also prepared via dichlorohydration of the alkynes using TClA.

With a selection of dihalohydroxyketones and dihalolactols in hand, we examined their reduction to access halogenated diols and cyclic ethers. Pleasingly, lactols **12a** and **13a** could be converted into the corresponding dihalo-1,4-diols **14/15** or dihalogenated tetrahydrofurans **16/17** through treatment with NaBH₄ or TFA/Et₃SiH respectively. Dichlorohydroxyketones **7n** and **7o** could readily be converted with high diastereoselectivity into the *anti*-dichlorodiols **18** via reduction with Me₄NB(OAc)₃H.^[14] The same procedure was also used to access *anti*-bromodiols **19**. We next set out to investigate a comple-

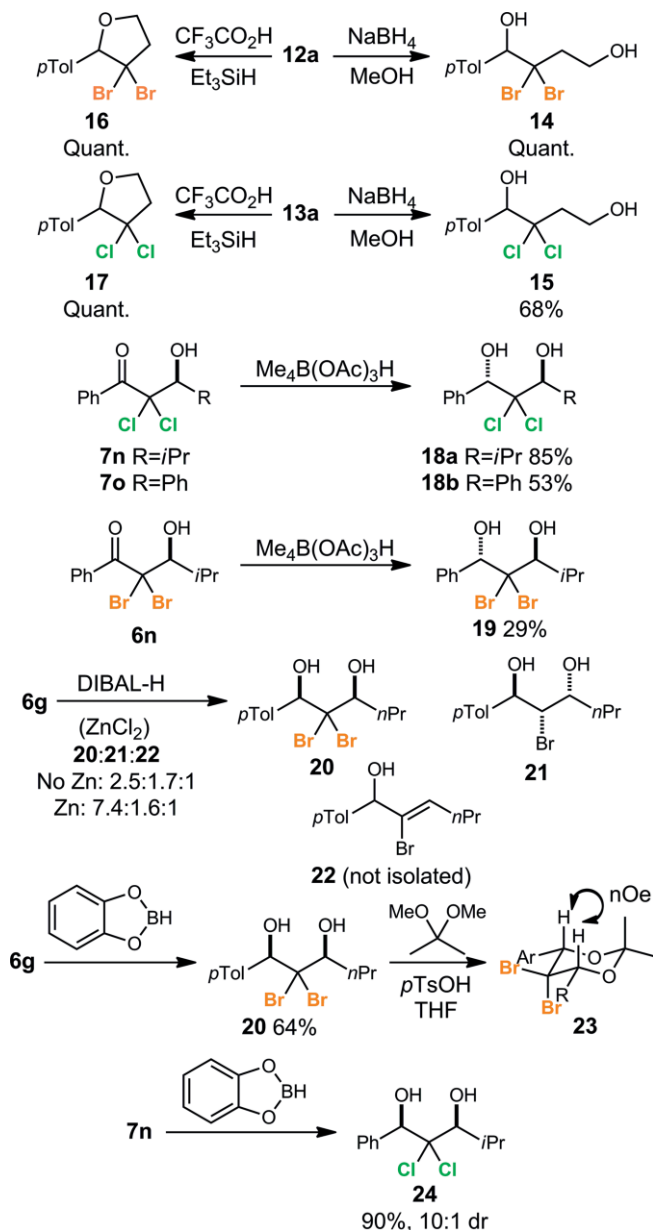


Scheme 4. Dibromohydration and dichlorohydration of extended alkynols.

mentary method to access the corresponding *syn*-dihalodols. Reduction of **6g** with DIBAL-H in the presence or absence of ZnCl₂^[15] led to the formation of a mixture of products including desired *syn*-diol **20**, monobrominated *anti*-diol **21**, and brominated allylic alcohol **22**, with the zinc chloride leading to an enhanced selectivity in favour of the desired diol **20**. An alternative reduction protocol using catechol borane^[16] gave a mixture of *syn* and *anti* diols in 82 % overall yield (82:18 *dr*), from which the desired *syn* diol **20** could be isolated in 64 % yield. The stereochemistry of **20** was confirmed through formation of the acetone **23** which displayed an *nOe* between the two axial protons indicated. Using the same method, dichlorohydroxyketone **7n** was converted into the corresponding *syn*-dichlorodiols **24** in 90 % yield. Interestingly, dibromo-1,3-diols such as **19** and **20** have never previously been synthesised (Scheme 5).^[17]

We envisaged that lactols such as **12a** could readily be converted into synthetically useful 3-halofurans^[18] through formal elimination of water and HX. Attempts to convert **12a** directly into the 3-bromofuran were unsuccessful. However, further investigation determined that 3-halofurans could be successfully obtained through conversion of the lactols **12a**, **13a** and **13d** into the mixed ketal derivatives **25a-25c** with AcCl/MeOH, followed by basic elimination of methanol and HX. Using this sequence, we were able to access 3-bromofuran **26a**, 3-chlorofuran **26b** and trisubstituted bromofuran **26c**; with complete control over the substitution pattern in the latter compound. This approach is complementary to routes employing ynones,^[18a,b,e] providing access to a different regioisomer of the 3-halofuran (Scheme 6).

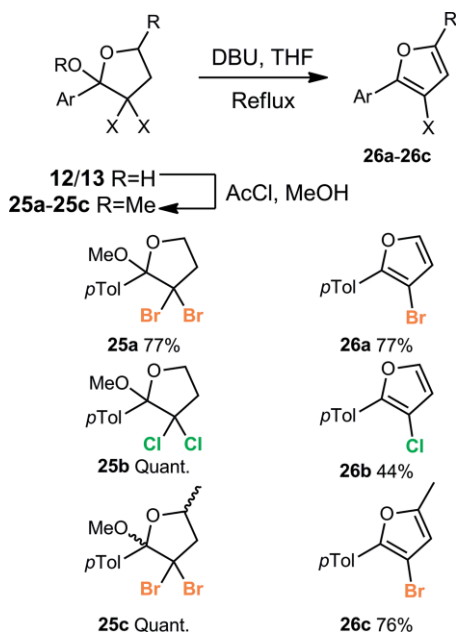
We have previously reported that 3-alkoxyfurans are readily able to undergo Diels–Alder reaction with maleimides to provide *endo*-cantharimide derivatives, which are promising lead-like molecules for medicinal chemistry.^[19] 3-Halofurans have been reported to show enhanced reactivity in intramolecular Diels–Alder reactions,^[20,21] so we were therefore interested in exploring their reactivity with maleimides to access useful halogenated cantharimide derivatives. 3-Bromofuran **26c** gave the



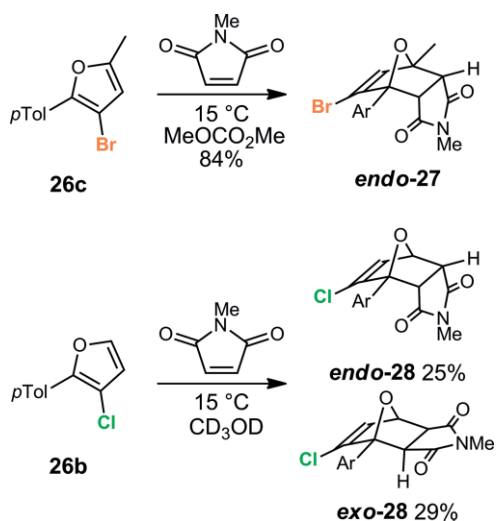
Scheme 5. Reduction of geminal dihalides to access halogenated diols and cyclic ethers.

endo cantharimide **27** as a single diastereoisomer in excellent yield upon reaction with *N*-methylmaleimide. However, 3-chlorofuran **26b** gave a mixture of the separable *endo* and *exo* cantharimides **28** in moderate overall yield under similar conditions (Scheme 7).

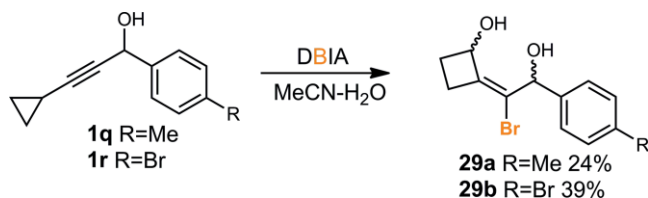
A further interesting transformation was uncovered upon attempted dibromination of cyclopropyl-containing propargylic alcohol **1q**, which yielded the vinylcyclobutane **29a** as the major product as a mixture of diastereoisomers. This reaction was extended to the synthesis of **29b**.^[22] Although ring expansion of cyclopropanes to cyclobutanes isprecedented,^[23] the direct ring expansion of cyclopropylacetylenes has rarely been observed (Scheme 8).^[24]



Scheme 6. Synthesis of 3-halofurans.



Scheme 7. Cycloaddition reactions of 3-halofurans.



Scheme 8. Synthesis of cyclobutanes via ring expansion of propargylic alcohols containing cyclopropylacetylenes.

Conclusions

We have reported a new method for the dibromohydration of alkynols to give dibromoketones that is applicable to a wide range of substrates, along with the extension of our previously

reported dichlorohydration reaction to new substrates. The dihaloketones obtained from these reactions can be used to prepare structurally diverse halogenated molecules including dihalodols, dihalogenated tetrahydrofurans, 3-halofurans, and halogenated cantharimides. We have also discovered a novel halogenation/ring expansion of alkenylcyclopropanes that provides alkenylcyclobutanes. Many of these classes of halogenated compound have never previously been prepared. Further work is underway to optimize these methods, and to explore the interesting properties of these structurally unusual molecules.

Experimental Section

Full experimental procedures for the preparation of all compounds, along with ¹H and ¹³C spectra for all novel compounds can be found in the supporting information.

General Procedure for Dibromohydration Reactions: Dibromoisocyanuric acid (1.1 equiv.) was added to a stirring solution of alkynyl alcohol (1.0 equiv.) in MeCN/H₂O (7:3, 2 mL mmol⁻¹). The solution was stirred for 10 min after which solvent was removed in vacuo and the resultant residue purified by column chromatography (10 % EtOAc in petrol) to give the dibromohydroxyketone.

General Procedure for Dichlorohydration Reactions: Trichloroisocyanuric acid (1 equiv.) was added to a stirring solution of alkynyl alcohol (1 equiv.) in MeCN/H₂O (10:1, 4 mL mmol⁻¹). After 30 min the solvent was removed in vacuo and the residue was purified by column chromatography to give the dichlorohydroxyketone.

2,2-Dibromo-3-hydroxy-1-phenylpropan-1-one (6a): 149 mg, 93 %, yellow oil. ¹H NMR (600 MHz, CDCl₃): δ = 8.40 (dd, *J* = 8.6, 1.2 Hz, 2 H, 2 × ArH), 7.61 (tt, *J* = 7.4, 1.2 Hz, 1 H, ArH), 7.49 (dd, *J* = 8.6, 7.4 Hz, 2 H, 2 × ArH), 4.35 (s, 2 H, CH₂), 3.12 (br. s, 1 H, OH) ppm. ¹³C NMR (150 MHz, CDCl₃): δ = 189.5, 134.3, 131.7, 131.4, 128.3, 72.1, 63.4 ppm. HRMS: Found (CI): [M + H]⁺ 306.89622, C₉H₉Br₂O₂: calcd. 306.89693. IR (film): ν_{max} = 3422 (O–H), 2918 (C–H), 1667 (C=O), 1446 (C=C) cm⁻¹. The synthesis of this compound has been previously reported using a different method.^[10b]

2,2-Dibromo-3-hydroxy-1-phenylhexan-1-one (6b): 818 mg, 74 %, yellow solid, m.p. 54–55 °C. ¹H NMR (CDCl₃, 600 MHz): δ = 8.37 (m, 2 H, ArH), 7.59 (m, 1 H, ArH), 7.48 (m, 2 H, ArH), 4.23 (dd, *J* = 9.6, 1.4 Hz, 1 H, CH), 3.34 (br. s, 1 H, OH), 2.07 (m, 1 H, 1 × CHCH₂), 1.80 (m, 1 H, 1 × CHCH₂), 1.74 (m, 1 H, 1 × CH₂CH₃), 1.52 (m, 1 H, 1 × CH₂CH₃), 1.02 (t, *J* = 7.4 Hz, 3 H, CH₃) ppm. ¹³C NMR (CDCl₃, 150 MHz): δ = 190.4, 133.9, 132.6, 131.5, 128.1, 77.2, 71.4, 34.9, 19.5, 14.1 ppm. LRMS (NSI): *m/z* = 375 (49, [M + Na]⁺, 2 × ⁸¹Br), 373 (100, [M + Na]⁺, ⁷⁹Br, ⁸¹Br), 371 (50, [M + Na]⁺, 2 × ⁷⁹Br). HRMS Found 370.9252, C₁₂H₁₄Br₂O₂Na ([M + Na]⁺): calcd. 370.9253. IR (solid): ν_{max} = 3544 (O–H), 2955 (C–H), 2927 (C–H), 2864 (C–H), 1667 (C=O), 1594 (C=C), 1574 (C=C), 1445 cm⁻¹.

2,2-Dibromo-3-ethyl-3-hydroxy-1-(*p*-tolyl)pentan-1-one (6c): 175 mg, 93 %, yellow oil. ¹H NMR (CDCl₃, 600 MHz): δ = 8.21 (d, *J* = 7.9 Hz, 2 H, ArH), 7.26 (d, *J* = 7.9 Hz, 2 H, ArH), 4.23 (br. s, 1 H, OH), 2.45 (s, 3 H, ArCH₃), 2.09 (q, *J* = 7.4 Hz, 4 H, 2 × CH₂CH₃), 1.09 (t, *J* = 7.4 Hz, 6 H, 2 × CH₂CH₃) ppm. ¹³C NMR (CDCl₃, 150 MHz): δ = 192.9, 144.6, 131.42, 131.38, 128.6, 80.8, 30.7, 21.8, 9.7 ppm. HRMS: Found 398.9553, C₁₄H₁₉Br₂O₂ ([M + H]⁺): calcd. 398.9566. IR (solid): ν_{max} = 3517 (O–H), 2969 (C–H), 2940 (C–H), 2879 (C–H), 1650 (C=O), 1603 (C=C), 1568 (C=C) cm⁻¹.

Ethyl 4,4-Dibromo-3-hydroxy-5-oxo-5-(*p*-tolyl)pentanoate (6d): 128 mg, 63 %, pale yellow oil. ¹H NMR (600 MHz, CDCl₃): δ = 8.28

54.4, 53.4, 22.4, 21.5, 21.4, 21.1 ppm. LRMS (CI) 370 (8 %, [M + NH₄]⁺, 2 × ⁸¹Br), 368 (20 %, [M + NH₄]⁺, ⁷⁹Br, ⁸¹Br), 366 (10 %, [M + NH₄]⁺, 2 × ⁷⁹Br), 335 (51 %, [M - CH₃]⁺, 2 × ⁸¹Br), 333 (100 %, [M - CH₃]⁺, ⁷⁹Br, ⁸¹Br), 331 (48 %, [M - CH₃]⁺, 2 × ⁷⁹Br). HRMS Found 365.9698, C₁₂H₁₈Br₂NO₂ ([M + NH₄]⁺): calcd. 365.9699. IR (film): $\tilde{\nu}_{\max}$ = 3342 (O-H), 2963 (C-H), 1913, 1510 (C=C) cm⁻¹.

3,3-Dichloro-2-(*p*-tolyl)tetrahydrofuran-2-ol (13a): Isolated as a mixture of isomers (1:8.3); 1.83 g, 83 %, white solid, m.p. 122–124 °C. ¹H NMR (CDCl₃, 500 MHz): δ = 8.22 (d, *J* = 8.4 Hz, 2 H, minor ArH), 7.65 (d, *J* = 8.2 Hz, 2 H, major ArH), 7.30 (d, *J* = 8.4 Hz, 2 H, minor ArH), 7.22 (d, *J* = 8.2 Hz, 2 H, major ArH), 4.24 (ddd, *J* = 9.2, 8.3, 7.1 Hz, 1 H, major 1 × OCH₂), 4.15 (ddd, *J* = 9.4, 8.3, 2.2 Hz, 1 H, major 1 × OCH₂), 3.99 (t, *J* = 6.3 Hz, 2 H, minor CH₂OH), 3.50 (br. s, 1 H, major OH), 3.20 (dt, *J* = 13.1, 9.3 Hz, 1 H, major 1 × CH₂CCl₂), 2.91 (ddd, *J* = 13.1, 7.1, 2.2 Hz, 1 H, major 1 × CH₂CCl₂), 2.84 (t, *J* = 6.3 Hz, 2 H, minor CH₂CCl₂), 2.47 (s, 3 H, minor CH₃), 2.41 (s, 3 H, major CH₃) ppm. ¹³C NMR (CDCl₃, 125 MHz): δ = 188.2, 145.0, 139.3, 134.4, 131.4, 129.0, 128.8, 128.5, 127.4, 105.9, 91.1, 85.4, 64.5, 59.3, 47.4, 44.4, 21.8, 21.3 ppm. LRMS (EI) 250 (12 %, M⁺, 2 × ³⁷Cl), 248 (67 %, M⁺, ³⁵Cl, ³⁷Cl), 246 (100 %, M⁺, 2 × ³⁵Cl), 229, 215, 194, 136. HRMS Found 246.02087, C₁₁H₁₂Cl₂O₂: calcd. 246.0209. IR (film): $\tilde{\nu}_{\max}$ = 3360 (O-H), 3036 (C-H), 2973 (C-H), 2926 (C-H), 2910 (C-H), 1608 (C=O), 1510, 1482 (C=C), 1441, 1400 cm⁻¹.

3,3-Dichloro-5-methyl-2-(*p*-tolyl)tetrahydrofuran-2-ol (13d): Isolated as a mixture of diastereomers (1:1.8); 463 mg, 89 %, pale yellow oil. ¹H NMR (CDCl₃, 600 MHz): δ = 7.67 (d, *J* = 8.1 Hz, 2 H, major ArH), 7.63 (d, *J* = 8.2 Hz, 2 H, minor ArH), 7.23–7.18 (m, 4 H, major ArH, minor ArH), 4.64–4.57 (m, 1 H, minor CH), 4.57–4.49 (m, 1 H, major CH), 3.29 (dd, *J* = 13.7, 9.2 Hz, 1 H, major 1 × CH₂), 3.16 (br. s, 1 H, major OH), 3.09 (br. s, 1 H, minor OH), 3.01 (dd, *J* = 13.0, 5.9 Hz, 1 H, minor 1 × CH₂), 2.88 (dd, *J* = 13.0, 9.5 Hz, 1 H, minor 1 × CH₂), 2.70 (dd, *J* = 13.7, 3.3 Hz, 1 H, major 1 × CH₂), 2.39 (s, 3 H, major ArCH₃), 2.38 (s, 3 H, minor ArCH₃), 1.49 (d, *J* = 6.4 Hz, 3 H, major CHCH₃), 1.47 (d, *J* = 6.3 Hz, 3 H, minor CHCH₃) ppm. ¹³C NMR (CDCl₃, 150 MHz): δ = 139.4, 139.4, 134.9, 134.6, 128.5, 128.5, 127.3, 127.3, 106.5, 106.1, 91.8, 91.2, 74.0, 72.0, 51.8, 51.0, 22.7, 21.4, 21.4, 21.2 ppm. LRMS (CI) 264 (1 %, [M + H]⁺, 2 × ³⁷Cl), 262 (5 %, [M + H]⁺, ³⁵Cl, ³⁷Cl), 260 (6 %, [M + H]⁺, 2 × ³⁵Cl), 247 (14 %, [M - CH₃]⁺), 245 (65 %, [M - CH₃]⁺), 243 (100 %, [M - CH₃]⁺).

Preparation of 1,4 diols: NaBH₄ (23 mg, 0.60 mmol) was added to a stirred solution of lactol **12/13** (0.50 mmol) in MeOH (4 mL) at 0 °C. After 10 min, NH₄Cl (5 mL) was added and the organic phase extracted with EtOAc (2 × 5 mL). The organic layer was washed with brine (2 × 5 mL), dried (MgSO₄), filtered and concentrated in vacuo. The resultant residue was purified by column chromatography (30 % EtOAc in petrol) to give the diol.

2,2-Dibromo-1-(*p*-tolyl)butane-1,4-diol (14): 198 mg, quantitative, white solid, m.p. 105–107 °C. ¹H NMR (CDCl₃, 600 MHz): δ = 7.47 (d, *J* = 8.0 Hz, 2 H, ArH), 7.18 (d, *J* = 8.0 Hz, 2 H, ArH), 5.01 (d, *J* = 1.9 Hz, 1 H, CH), 4.11–4.00 (m, 2 H, CH₂OH), 3.84 (d, *J* = 1.6 Hz, 1 H, CHO), 2.76 (dt, *J* = 15.0, 6.4 Hz, 1 H, 1 × CH₂CBr₂), 2.63 (dt, *J* = 15.0, 5.7 Hz, 1 H, 1 × CH₂CBr₂), 3.04 (s, 3 H, CH₃), 2.26 (s, 1 H, CH₂OH) ppm. ¹³C NMR (CDCl₃, 150 MHz): δ = 138.9, 134.1, 129.1, 128.6, 82.3, 79.4, 61.7, 48.1, 21.4 ppm. LRMS (EI) 340 (42 %, M⁺, 2 × ⁸¹Br), 338 (84 %, M⁺, ⁷⁹Br, ⁸¹Br), 336 (41 %, M⁺, 2 × ⁸¹Br), 160 (100 %). HRMS Found 335.9352, C₁₁H₁₄Br₂O₂: calcd. 335.9355. IR (film): $\tilde{\nu}_{\max}$ = 3338 (O-H), 2902 (C-H), 1515 (C=C) cm⁻¹.

2,2-Dichloro-1-(*p*-tolyl)butane-1,4-diol (15): 84 mg, 68 %, white solid, m.p. 92–93 °C. ¹H NMR (CDCl₃, 600 MHz): δ = 7.42 (d, *J* = 8.0 Hz, 2 H, ArH), 7.18 (d, *J* = 8.0 Hz, 2 H, ArH), 5.01 (s, 1 H, CH), 4.07–3.95 (m, 2 H, CH₂CCl₂), 2.61 (ddd, *J* = 15.0, 7.1, 5.6 Hz, 1 H, 1 ×

CH₂CBr₂), 2.54 (s, 1 H, CH₂OH), 2.45 (dt, *J* = 15.0, 5.5 Hz, 1 H, 1 × CH₂CCl₂), 2.37 (s, 3 H, CH₃) ppm. ¹³C NMR (CDCl₃, 150 MHz): δ = 138.8, 133.8, 128.9, 128.6, 95.5, 81.2, 59.4, 46.1, 21.4 ppm. LRMS (EI) 252 (1 %, [M]⁺, 2 × ³⁷Cl), 250 (5 %, [M]⁺, ³⁵Cl, ³⁷Cl), 248 (7 %, [M]⁺, 2 × ³⁵Cl), 167 (6 %), 149 (11 %), 121 (100 %). HRMS Found 248.0365, C₁₁H₁₄Cl₂O₂: calcd. 248.0365. IR (film): $\tilde{\nu}_{\max}$ = 3220 (O-H), 2900 (C-H), 2849 (C-H) cm⁻¹.

Preparation of Dihalogenated Cyclic Ethers: Using flame dried glassware and under an argon atmosphere, BF₃·OEt₂ (213 mg, 1.50 mmol) was added to a solution of lactol **12** (0.50 mmol) and Et₃SiH (116 mg, 1.00 mmol) in CH₂Cl₂ (1 mL) at –78 °C. The reaction was stirred at –78 °C for 5 min and then warmed to room temperature over 30 min. Solvent was removed in vacuo and the resultant residue purified by column chromatography (10 % EtOAc in petrol).

3,3-Dibromo-2-(*p*-tolyl)tetrahydrofuran (16): 158 mg, quantitative, colourless oil. ¹H NMR (CDCl₃, 600 MHz): δ = 7.49 (d, *J* = 8.1 Hz, 2 H, ArH), 7.21 (d, *J* = 8.1 Hz, 2 H, ArH), 5.02 (s, 1 H, ArCH), 4.29 (td, *J* = 8.5, 7.4 Hz, 1 H, 1 × CH₂O), 4.16–4.07 (m, 1 H, 1 × CH₂O), 3.23–3.16 (m, 2 H, CH₂CBr₂), 2.39 (s, 3 H, CH₃) ppm. ¹³C NMR (CDCl₃, 150 MHz): δ = 138.8, 133.2, 128.6, 127.5, 90.7, 66.8, 65.7, 50.2, 21.5 ppm. LRMS (APCI+) 323 (34 %, [M + H]⁺, 2 × ⁸¹Br), 321 (42 %, [M + H]⁺, ⁷⁹Br, ⁸¹Br), 319 (30 %, [M + H]⁺, 2 × ⁷⁹Br), 305 (34 %, [M + H - H₂O]⁺, 2 × ⁸¹Br), 303 (61 %, [M + H - H₂O]⁺, ⁷⁹Br, ⁸¹Br), 301 (34 %, [M + H - H₂O]⁺, 2 × ⁷⁹Br), 241 (100 %, [M + H - Br]⁺, ⁸¹Br), 239 (96 %, [M + H - Br]⁺, ⁷⁹Br). HRMS Found 300.9225, C₁₁H₁₁Br₂ ([M + H - H₂O]⁺): calcd. 300.9228. IR (film): $\tilde{\nu}_{\max}$ = 2953 (C-H), 2892 (C-H) cm⁻¹.

3,3-Dichloro-2-(*p*-tolyl)tetrahydrofuran (17): 118 mg, quantitative, colourless oil. ¹H NMR (CDCl₃, 600 MHz): δ = 7.45 (d, *J* = 8.0 Hz, 2 H, ArH), 7.24 (d, *J* = 8.0 Hz, 2 H, ArH), 5.10 (s, 1 H, CH), 4.30 (td, *J* = 8.6, 7.2 Hz, 1 H, 1 × CH₂O), 4.21 (td, *J* = 8.6, 3.7 Hz, 1 H, 1 × CH₂O), 3.02 (ddd, *J* = 13.5, 7.2, 3.7 Hz, 1 H, 1 × CH₂CCl₂), 2.96 (dt, *J* = 13.5, 8.9 Hz, 1 H, 1 × CH₂CCl₂), 2.41 (s, 3 H, CH₃) ppm. ¹³C NMR (CDCl₃, 150 MHz): δ = 138.7, 132.1, 128.7, 127.5, 89.7, 89.7, 65.5, 47.7, 21.5 ppm. LRMS (EI) 234 (11 %, [M]⁺, 2 × ³⁷Cl), 232 (58 %, [M]⁺, ³⁵Cl, ³⁷Cl), 230 (100 %, [M]⁺, 2 × ³⁵Cl), 215 (34 %), 217 (24 %), 194 (44 %). HRMS Found 230.02585, C₁₁H₁₂Cl₂O: calcd. 230.02597. IR (film): $\tilde{\nu}_{\max}$ = 2953 (C-H), 2894 (C-H) cm⁻¹.

2,2-Dichloro-4-methyl-1-phenylpentane-1,3-diol (18a): Ketone **7n** (131 mg, 0.5 mmol) was added to a stirring solution of NMe₄HB(OAc)₃ (8 equiv.) under argon atmosphere in MeCN (0.75 mL) and glacial AcOH (0.75 mL) at –40 °C. After 1 h, the reaction mixture was washed with saturated NaHCO₃ solution (10 mL) and extracted with CH₂Cl₂ (10 mL × 3). The combined organic phases were dried with MgSO₄ and concentrated under reduced pressure which afforded the *anti* diol as a yellow oil (112.6 mg, 85 %). ¹H NMR (CDCl₃, 400 MHz): δ = 7.56–7.55 (m, 2 H, ArH), 7.39–7.37 (m, 3 H, ArH), 5.29 [s, 1 H, PhCH(Cl)₂], 4.10 (d, *J* = 5.3 Hz, 1 H, OH), 3.48 (s, 1 H, OH), 2.79 [d, *J* = 8.0 Hz, 1 H, CHCH(CH₃)₂], 2.46 [heptd, *J* = 7.0, 2.8 Hz, 1 H, CH(CH₃)₂], 1.14 [d, *J* = 3.0 Hz, 3 H, CH(CH₃)₂], 1.12 [d, *J* = 3.0 Hz, 3 H, CH(CH₃)₂] ppm. ¹³C NMR (CDCl₃, 176 MHz): δ = 137.3, 129.3, 128.8, 127.7, 97.2, 80.0, 79.1, 29.8, 23.1, 16.8 ppm. LRMS (ES+) 262.1 (90 %, [M - H]⁺), 263.1 (55 %, [M]⁺). HRMS Found 285.0421, C₁₂H₁₆Cl₂O₂Na: calcd. 285.0420 ([M + Na]⁺). IR (film): $\tilde{\nu}_{\max}$ = 3405.17 (O-H), 2961.23 (C-H), 2928.81 (C-H), 2871.73 (C-H), 1452.12, 1049.77, 698.36 cm⁻¹.

2,2-Dichloro-1,3-diphenylpropane-1,3-diol (18b): Prepared according to the same procedure as **18a**. Purified via column chromatography (30 % EtOAc in Petrol) which afforded diol **18b** as a White solid (53 mg, 53 %, m.p. 94–96 °C). ¹H NMR (600 MHz, CDCl₃): δ = 7.57 (br. m, 4 H, ArH), 7.40–7.39 (m, 6 H, ArH), 5.34 (d, *J* = 4.5 Hz, 2

H, *CHOH*), 3.48 (d, $J = 4.7$ Hz, 2 H, OH) ppm. ^{13}C NMR (151 MHz, CDCl_3): $\delta = 137.1, 129.2, 129.1, 127.9, 79.5$ ppm. LRMS (NSI) 319 (100 %, $[\text{M} + \text{Na}]^+$, $2 \times ^{35}\text{Cl}$), 321 (60 %, $[\text{M} + \text{Na}]^+$, $^{35}\text{Cl}, ^{37}\text{Cl}$), 323 (10 %, $[\text{M} + \text{Na}]^+$, $2 \times ^{37}\text{Cl}$). HRMS Found 319.0263: calcd. 319.0266 ($[\text{M} + \text{Na}]^+$). IR (film): $\tilde{\nu}_{\text{max}} = 3388$ (O–H), 3060 (C–H), 2920 (C–H), 1452, 1026, 907, 698, 670 cm^{-1} .

anti-2,2-Dibromo-4-methyl-1-phenylpentane-1,3-diol (19): Prepared according to the same procedure as **18a**: purified via column chromatography (20–70 % EtOAc/Petrol) which afforded **19** as white crystals (31 mg, 0.09 mmol, 29 %); m.p. 79–82 °C. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.63\text{--}7.59$ (m, 2 H, ArH), 7.39–7.36 (m, 3 H, ArH), 5.19 [d, $J = 4.8$ Hz, 1 H, $\text{PhCH}(\text{Br})_2$], 4.03 [dd, $J = 7.9, 2.2$ Hz, 1 H, $\text{CH}(\text{OH})\text{CH}$], 3.61 (d, $J = 5.0$ Hz, 1 H, OH), 2.86 (d, $J = 7.9$ Hz, 1 H, OH), 2.54 [heptd, $J = 6.9, 2.2$ Hz, 1 H, $\text{CH}(\text{CH}_3)_2$], 1.15 [d, $J = 6.8$ Hz, $\text{CH}(\text{CH}_3)_2$], 1.13 [d, $J = 7.0$ Hz, 3 H, $\text{CH}(\text{CH}_3)_2$] ppm. ^{13}C NMR (151 MHz, CDCl_3): $\delta = 138.0$ (C), 129.6 (CH), 128.9 (CH), 127.6 (CH), 85.0 (C), 81.3 (CH), 80.1 (CH), 31.2 (CH), 23.8 (CH₃), 16.9 (CH₃) ppm. LRMS (ES+) 373 (51 %, $[\text{M} + \text{Na}]^+$, $2 \times ^{79}\text{Br}$), 375 (100 %, $[\text{M} + \text{Na}]^+$, $^{79}\text{Br}, ^{81}\text{Br}$), 377 (45 %, $[\text{M} + \text{Na}]^+$, $2 \times ^{81}\text{Br}$). HRMS (ES+) Found 372.9417, $\text{C}_{12}\text{H}_{16}\text{Br}_2\text{O}_2\text{Na}$: calcd. 372.9409 ($[\text{M} + \text{Na}]^+$). IR (film): $\tilde{\nu}_{\text{max}} = 3389$ (O–H), 2961 (C–H), 2869 (C–H), 1083 (C–O), 733 (C–Br) cm^{-1} .

(±)-(1S,3R)-2,2-Dibromo-1-(*p*-tolyl)hexane-1,3-diol (20) and 2-Bromo-1-(*p*-tolyl)hexane-1,3-diol (21): Method A: Using flame dried glassware and under an argon atmosphere, **6g** (36 mg, 0.10 mmol) was dissolved in THF (1 mL) and cooled to –78 °C. $\text{ZnCl}_2\text{-TMEDA}$ (25 mg, 0.10 mmol) was added, followed by DIBAL-H (1 M in hexanes, 300 μL , 0.300 mmol). The reaction was stirred at –78 °C for 1 h. The reaction mixture was poured into a mixture of HCl (6 M, 2 mL) and sat. NH_4Cl (2 mL). The organic layer was extracted with Et_2O (3 \times 1 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The resultant residue was purified by column chromatography (10 % EtOAc in petrol).

Method B: Using flame dried glassware and under an argon atmosphere, **6g** (36 mg, 0.10 mmol) was dissolved in THF (1 mL) and cooled to –78 °C. DIBAL-H (1 M in hexanes, 300 μL , 0.300 mmol) was added. The reaction was stirred at –78 °C for 1 h. The reaction mixture was poured into a mixture of HCl (6 M, 2 mL) and sat. NH_4Cl (2 mL). The organic layer was extracted with Et_2O (3 \times 1 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The resultant residue was purified by column chromatography (10 % EtOAc in petrol).

2-Bromo-1-(*p*-tolyl)hexane-1,3-diol (21): Method A: 7 mg, 24 μmol , 24 %; Method B: 5 mg, 17 μmol , 17 %. ^1H NMR (CDCl_3 , 600 MHz): $\delta = 7.29$ (d, $J = 8.1$ Hz, 2 H, ArH), 7.19 (d, $J = 8.1$ Hz, 2 H, ArH), 5.01 (d, $J = 6.2$ Hz, 1 H, ArCH), 4.22 (dd, $J = 6.2, 1.7$ Hz, 1 H, CHBr), 3.48 (br. t, $J = 6.2$ Hz, 1 H, CHCH_2), 3.07 (br. s, 1 H, OH), 2.07 (br. s, 1 H, OH), 2.63 (s, 3 H, ArCH_3), 1.68–1.55 (m, 1 H, $1 \times \text{CHCH}_2$), 1.55–1.44 (m, 1 H, $1 \times \text{CHCH}_2$), 1.44–1.23 (m, 2 H, CH_2CH_3), 0.88 (t, $J = 7.4$ Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (CDCl_3 , 150 MHz): $\delta = 138.3, 137.2, 129.4, 126.5, 76.3, 72.3, 70.6, 39.0, 21.3, 18.7, 14.0$ ppm. LRMS (CI) 306 (96 %, $[\text{M} + \text{NH}_4]^+$, ^{81}Br), 304 (100 %, $[\text{M} + \text{NH}_4]^+$, ^{79}Br), 288 (25 %, M^+ , ^{81}Br), 286 (28 %, M^+ , ^{79}Br). HRMS Found 286.0563, $\text{C}_{13}\text{H}_{19}\text{BrO}_2$: calcd. 286.0563. IR (film): $\tilde{\nu}_{\text{max}} = 3351$ (O–H), 2962 (C–H), 2923 (C–H), 1511, 1461 cm^{-1} .

2,2-Dibromo-1-(*p*-tolyl)hexane-1,3-diol (20): Using flame dried glassware and under an argon atmosphere, catecholborane (1 M in THF, 10 mL, 10 mmol) was added to a stirring solution of **6g** (182 mg, 0.5 mmol) in THF (35 mL) at –10 °C. The reaction was stirred at –10 °C for 6 h. MeOH (10 mL), saturated sodium potassium tartrate (10 mL) and pinacol (750 mg, 6.36 mmol) were added and

the reaction was stirred for 18 h at room temperature. The reaction mixture was diluted with EtOAc (30 mL) and washed with NaOH (0.5 M) until the aqueous layer was colourless. The organic layer was washed with brine (2 \times 50 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The resultant residue was purified by column chromatography (20 % EtOAc in petrol) to give **20** as a colourless oil (117 mg, 64 %). ^1H NMR (CDCl_3 , 600 MHz): $\delta = 7.52$ (d, $J = 8.1$ Hz, 2 H, ArH), 7.18 (d, $J = 8.1$ Hz, 2 H, ArH), 5.21 (s, 1 H, ArCH), 3.42 (br. t, $J = 8.0$ Hz, 1 H, CHCH_2), 3.31 (br. s, 1 H, OH), 2.36 (s, 3 H, ArCH_3), 2.23–2.14 (br. d, $J = 7.5$ Hz, 1 H, OH), 2.19 (m, 1 H, $1 \times \text{CHCH}_2$), 1.68 (dtd, $J = 14.3, 9.7, 4.8$ Hz, 1 H, $1 \times \text{CHCH}_2$), 1.64–1.53 (m, 1 H, $1 \times \text{CH}_2\text{CH}_3$), 1.41–1.33 (m, 1 H, $1 \times \text{CH}_2\text{CH}_3$), 0.93 (t, $J = 7.4$ Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (CDCl_3 , 150 MHz): $\delta = 138.8, 134.6, 128.8, 128.7, 90.8, 80.0, 77.7, 37.3, 21.4, 19.2, 14.0$ ppm. LRMS (NSI) 386 (50 %, $[\text{M} + \text{NH}_4]^+$, $2 \times ^{81}\text{Br}$), 384 (100 %, $[\text{M} + \text{NH}_4]^+$, $^{79}\text{Br}, ^{81}\text{Br}$), 382 (52 %, $[\text{M} + \text{NH}_4]^+$, $2 \times ^{79}\text{Br}$) 227 (41 %). HRMS Found 382.0016, $[\text{C}_{13}\text{H}_{18}\text{Br}_2\text{O}_2 + \text{NH}_4]^+$: calcd. 382.0012. IR (film): $\tilde{\nu}_{\text{max}} = 3274$ (O–H), 2959 (C–H), 2928 (C–H), 1516 (C=C), 1453 cm^{-1} .

(±)-(4R,6S)-5,5-Dibromo-2,2-dimethyl-4-propyl-6-(*p*-tolyl)-1,3-dioxane (23) and (±)-(4R,6S)-5-Bromo-2,2-dimethyl-4-propyl-6-(*p*-tolyl)-1,3-dioxane (23b): Using flame dried glassware and under an argon atmosphere, **20** (7 mg, 19 μmol) was dissolved in THF (1 mL). *p*-Toluenesulfonic acid (4 mg, 21 μmol) was added, followed by 2,2-dimethoxypropane (20 mg, 19 μmol). The reaction was refluxed for 18 h. The reaction mixture was diluted with sat. sodium hydrogen carbonate (1 mL) and extracted with Et_2O (2 \times 1 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The resultant residue was purified by column chromatography (2 % EtOAc in petrol) to give **23** and **23b** as a colourless film in a 1:1.3 ratio (4 mg). ^1H NMR (CDCl_3 , 600 MHz): $\delta = 7.53$ (d, $J = 8.2$ Hz, 2 H, 23 ArH), 7.32 (d, $J = 8.1$ Hz, 2 H, 23b ArH), 7.20–7.15 (m, 4 H, 23 ArH, 23b ArH), 4.94 (s, 1 H, 23 ArCH), 4.82 (d, $J = 10.3$ Hz, 1 H, 23b ArCH), 4.03 (ddd, $J = 10.4, 8.4, 2.3$ Hz, 1 H, 23b CHCH_2), 3.89 (dd, $J = 9.3, 1.7$ Hz, 1 H, 23 CHCH_2), 3.69 (t, $J = 10.4$ Hz, 1 H, 23b CHBr), 2.37 (s, 3 H, 23 ArCH_3), 2.35 (s, 3 H, 23b ArCH_3), 2.11–2.01 (m, 1 H, 23 $1 \times \text{CHCH}_2$), 1.95 (ddd, $J = 9.9, 5.8, 5.0, 2.1$ Hz, 1 H, 23b $1 \times \text{CHCH}_2$), 1.78 (dtd, $J = 14.1, 9.4, 4.8$ Hz, 1 H, 23 $1 \times \text{CHCH}_2$), 1.61 [s, 3 H, 23b $1 \times \text{C}(\text{CH}_3)_2$], 1.57 [s, 3 H, 23 $1 \times \text{C}(\text{CH}_3)_2$], 1.56 [s, 3 H, 23 $1 \times \text{C}(\text{CH}_3)_2$], 1.55–1.49 (m, 1 H, B $1 \times \text{CHCH}_2$), 1.46 [s, 3 H, 23b $1 \times \text{C}(\text{CH}_3)_2$], 1.45–1.36 (m, 2 H, 23 CH_2CH_3), 0.99 (t, $J = 7.4$ Hz, 3 H, 23 CH_2CH_3), 0.95 (t, 3 H, 23b CH_2CH_3) ppm. ^{13}C NMR (CDCl_3 , 150 MHz): $\delta = 138.8, 138.6, 136.1$ (23b), 132.9 (23), 129.7 (23), 129.1 (23b), 128.0 (23b), 127.9 (23b), 100.6 (23), 99.8 (23b), 81.0 (23) 79.4 (23), 77.9 (23), 74.0 (23b), 55.0 (23b), 35.5 (23b), 34.7 (23), 29.9, 29.6, 21.4, 21.4, 19.7, 19.4, 19.1, 18.1, 13.9, 13.9 ppm. LRMS (CI) 426 (49 %, $[\text{MA} + \text{NH}_4]^+$, $2 \times ^{81}\text{Br}$), 424 (100 %, $[\text{MA} + \text{NH}_4]^+$, $^{79}\text{Br}, ^{81}\text{Br}$), 422 (51 %, $[\text{MA} + \text{NH}_4]^+$, $2 \times ^{81}\text{Br}$), 368 (23 %), 366 (48 %), 364 (48 %), 346 (11 %, $[\text{MB} + \text{NH}_4]^+$, ^{81}Br), 344 (11 %, $[\text{MB} + \text{NH}_4]^+$, ^{79}Br), 312 (87 %, $[\text{MB} - \text{CH}_3]^+$, ^{81}Br), 310 (85 %, $[\text{MB} - \text{CH}_3]^+$, ^{79}Br), 296 (47 %), 294 (50 %), 279 (54 %), 277 (54 %). HRMS Found 422.0325, $[\text{C}_{16}\text{H}_{23}\text{Br}_2\text{O}_2 + \text{NH}_4]^+$: calcd. 422.0325. IR (film): $\tilde{\nu}_{\text{max}} = 2955$ (C–H), 2919 (C–H), 2868 (C–H), 2850 (C–H), 1513, 1455 cm^{-1} .

An nOe was observed between the methine protons on the six-membered ring in acetal **23**, confirming the *syn* stereochemistry of the diol.

2,2-Dichloro-4-methyl-1-phenylpentane-1,3-diol (24): In flame dried glassware and under an argon atmosphere, catecholborane (1 M in THF, 8 mL, 8 mmol) was added to a stirring solution of **7a** (261 mg, 1 mmol) in THF (26 mL) at –10 °C. The reaction was stirred at –10 °C for 2 h 30 min. MeOH (8 mL), saturated sodium potassium tartrate (8 mL) and pinacol (568 mg) were added and the reaction was stirred for 20 h at room temp. The reaction mixture was diluted

endo-28: 5.8 mg, 25 %, white solid, m.p. 106–109 °C. ¹H NMR ([D₄]MeOD, 600 MHz): δ = 7.70 (d, *J* = 8.2 Hz, 2 H, ArH), 7.26 (d, *J* = 8.2 Hz, 2 H, ArH), 6.46 (d, *J* = 2.0 Hz, 1 H, C=CH), 5.37 (dd, *J* = 5.5, 2.0 Hz, 1 H, OCH), 3.91 (dd, *J* = 7.5, 5.5 Hz, 1 H, OCHCH), 3.79 (d, *J* = 7.5 Hz, 1 H, ArCCH), 2.87 (s, 3 H, NCH₃), 2.38 (s, 3 H, ArCH₃) ppm. ¹³C NMR ([D₄]MeOD, 150 MHz): δ = 176.4, 175.3, 142.0, 140.1, 132.7, 130.2, 129.9, 128.9, 94.5, 79.7, 51.6, 51.2, 24.9, 21.3 ppm. LRMS (CI) 323 (40 %, [M + NH₄]⁺, ³⁷Cl), 321 (100 %, [M + NH₄]⁺, ³⁵Cl), 193 (17 %). HRMS Found 321.1001, C₁₆H₁₈ClN₂O₃⁺ ([M + NH₄]⁺): calcd. 321.1000. IR (film): ν_{max} = 2922 (C–H), 1772, 1689 (C=O), 1589, 1519 cm⁻¹.

exo-28: 6.6 mg, 29 %, white solid, m.p. 143–144 °C. ¹H NMR ([D₄]MeOD, 600 MHz): δ = 7.42 (d, *J* = 8.2 Hz, 2 H, ArH), 7.21 (d, *J* = 8.2 Hz, 2 H, ArH), 6.57 (d, *J* = 2.1 Hz, 1 H, C=CH), 5.31 (d, *J* = 2.1 Hz, 1 H, OCH), 3.53 (d, *J* = 6.4 Hz, 1 H, OCHCH), 3.37 (d, *J* = 6.4 Hz, 1 H, ArCCH), 2.79 (s, 3 H, NCH₃), 2.36 (s, 3 H, ArCH₃) ppm. ¹³C NMR ([D₄]MeOD, 150 MHz): δ = 177.5, 175.2, 144.7, 139.5, 132.0, 130.0, 129.3, 128.3, 95.0, 81.7, 53.6, 50.0, 24.9, 21.3 ppm. LRMS (CI) 323 (40 %, [M + NH₄]⁺, ³⁷Cl), 321 (100 %, [M + NH₄]⁺, ³⁵Cl), 193 (18 %). HRMS Found 321.1001, C₁₆H₁₈ClN₂O₃: calcd. 321.1000. IR (film): ν_{max} = 2920 (C–H), 1764, 1687 (C=O), 1591, 1519 cm⁻¹.

Preparation of Halogenated Cyclobutanols: Dibromoisocyanuric acid (0.6 equiv.) was added to a stirring solution of propargylic alcohol **1q** or **1r** (1.0 equiv.) in MeCN/H₂O (7:3, 8.5 mL mmol⁻¹). The solution was stirred for 1 h. Saturated Na₂S₂O₃ was added and the mixture extracted with EtOAc. The organic layers were dried (MgSO₄), filtered and concentrated in vacuo. The resultant residue was purified by column chromatography (10 % EtOAc in petrol) to give the cyclobutane products.

(E)-2-[1-Bromo-2-hydroxy-2-(p-tolyl)ethylidene]cyclobutan-1-ol (29a): Isolated as a mixture of diastereomers (1:1.6); 168 mg, 24 %, pale yellow oil. ¹H NMR (CDCl₃, 600 MHz): δ = 7.35 (d, 8.1, 2 H, minor ArH), 7.33 (d, *J* = 8.1 Hz, 2 H, major ArH), 7.19 (d, *J* = 8.1 Hz, 4 H, minor ArH, major ArH), 5.54 (br. d, *J* = 3.6 Hz, 1 H, major ArCH), 5.52 (br. s, 1 H, minor ArCH), 4.97–4.89 (m, 2 H, major CH₂CH, minor CH₂CH), 3.58 (br. d, *J* = 5.7 Hz, 1 H, OH), 3.50 (br. d, *J* = 3.6 Hz, 1 H, OH), 3.48 (br. s, 1 H, OH), 3.28 (br. s, 1 H, OH), 2.63–2.48 (m, 2 H, major 1 × C=CCH₂, minor 1 × C=CCH₂), 2.42–2.29 (m, 4 H, major 2 × CHCH₂, minor 2 × CHCH₂), 2.36 (s, 6 H, major CH₃, minor CH₃) ppm. ¹³C NMR (150 MHz, CDCl₃): δ = 144.7 (major), 144.7 (minor), 138.3, 138.2, 138.0, 137.9, 129.4, 127.0 (major), 126.9 (minor), 121.7 (minor), 120.5 (major), 76.3, 75.9, 70.9, 70.5, 27.5, 27.2, 25.8, 25.3, 21.4 ppm. LRMS (CI) 284 (96 %, [M]⁺, ⁸¹Br), 282 (100 %, [M]⁺, ⁷⁹Br), 267 (17 %, [M – OH]⁺, ⁸¹Br), 265 (18 %, [M – OH]⁺, ⁷⁹Br), 185 (19 %). HRMS Found 282.02508, C₁₃H₁₅BrO₂: calcd. 282.02499. IR (film): ν_{max} = 3313 (O–H), 2977 (C–H), 2945 (C–H), 2917 (C–H), 1683, 1510, 1418 cm⁻¹; Relative geometry assigned by analogy to **29b** below.

(E)-2-[1-Bromo-2-hydroxy-2-(p-tolyl)ethylidene]cyclobutan-1-ol (29b): Isolated as a mixture of diastereomers (1:1.1); 68 mg, 39 %, pale yellow oil. ¹H NMR (CDCl₃, 600 MHz): δ = 7.51–7.50 (m, 2 H, major ArH), 7.50–7.48 (m, 2 H, minor ArH), 7.36 (d, *J* = 8.2 Hz, 2 H, minor ArH), 7.31 (d, *J* = 8.2 Hz, 2 H, major ArH), 5.57 (s, 1 H, minor ArCH), 5.56 (s, 1 H, major ArCH), 4.98–4.90 (m, 2 H, major CH₂CH, minor CH₂CH), 2.61–2.49 (m, 2 H, major 1 × C=CCH₂, minor 1 × C=CCH₂), 2.42–2.30 (m, 4 H, major 1 × C=CCH₂, major 1 × CHCH₂, minor 1 × C=CCH₂, minor 1 × CHCH₂), 2.05–1.94 (m, 2 H, major 1 × CHCH₂, minor 1 × CHCH₂) ppm. ¹³C NMR (CDCl₃, 150 MHz): δ = 145.4 (minor), 145.3 (major), 140.0 (minor), 139.9 (major), 131.8 (major), 131.7 (minor), 128.8 (major), 128.7 (minor), 122.3 (major), 122.3 (minor), 121.6 (minor), 120.2 (major), 75.1 (major), 75.1 (minor), 70.9 (major), 70.6 (minor), 27.7 (major), 27.6 (minor), 25.7 (minor), 25.2 (major) ppm. LRMS (NSI) 373 (51 %,

[M + Na]⁺, 2 × ⁸¹Br), 371 (100 %, [M + Na]⁺, ⁸¹Br, ⁷⁹Br), 369 (49 %, [M + Na]⁺, 2 × ⁷⁹Br), HRMS Found 370.9076. C₁₂H₁₂Br₂O₂Na requires 370.9076. IR (film): ν_{max} = 3313 (O–H), 2947 (C–H), 1691, 1591 cm⁻¹. Relative geometry assigned based on NOESY spectra with key correlations indicated (See supporting information, Figure S1).

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- [1] a) P. Jeschke, *Pest. Manag. Sci.* **2010**, *66*, 10; b) P. Jeschke, *Pest. Manag. Sci.* **2017**, *73*, 1053.
- [2] E. S. Beach, B. R. Weeks, R. Stern, P. T. Anastas, *Pure Appl. Chem.* **2013**, *85*, 1611; K. D'Silva, A. Fernandes, M. Rose, *Crit. Rev. Environ. Sci. Technol.* **2004**, *34*, 141.
- [3] a) P. G. Gildner, T. J. Colacot, *Organometallics* **2015**, *34*, 5497; b) I. Hussain, J. Capricho, M. A. Yawer, *Adv. Synth. Catal.* **2016**, *358*, 3320.
- [4] a) L. T. Scott, W. D. Cotton, *J. Am. Chem. Soc.* **1973**, *95*, 2708; b) T. Okazoe, K. Takai, K. Utimoto, *J. Am. Chem. Soc.* **1987**, *109*, 951.
- [5] a) A. Takahashi, M. Shibasaki, *J. Org. Chem.* **1988**, *53*, 1227; b) C. Peppe, R. Pavão das Chagas, *Synlett* **2006**, 605; For use in [4+3] cycloadditions, see: c) R. S. Grainger, R. B. Owoare, P. Tiselli, J. W. Steed, *J. Org. Chem.* **2003**, *68*, 7899; d) S. Sendelbach, R. Schwetzer-Raschke, A. Radl, R. Kaiser, G. H. Henle, H. Korfant, S. Reiner, B. Föhlich, *J. Org. Chem.* **1999**, *64*, 3398.
- [6] a) D. E. Armstrong, D. H. Richardson, *J. Chem. Soc.* **1933**, 496; b) T. Takeda, R. Sasaki, A. Nakamura, S. Yamauchi, T. Fujiwara, *Synlett* **1996**, 273; c) D. J. Dixon, S. V. Ley, S. Lohmann, T. D. Sheppard, *Synlett* **2005**, 481.
- [7] L. Aufavre, P. Knochel, I. Marek, *Chem. Commun.* **1999**, 2207.
- [8] J. M. D'Oyley, A. E. Aliev, T. D. Sheppard, *Angew. Chem. Int. Ed.* **2014**, *53*, 10747; *Angew. Chem.* **2014**, *126*, 10923.
- [9] a) G. A. Hiegel, C. D. Bayne, B. Ridley, *Synth. Commun.* **2003**, *33*, 1997; b) J. Liu, W. Li, C. Wang, Y. Li, Z. Li, *Tetrahedron Lett.* **2011**, *52*, 4320; c) S. Madabhushi, R. Jillella, K. K. R. Mallu, K. R. Godala, V. S. Vangipuram, *Tetrahedron Lett.* **2013**, *54*, 3993; d) C. Shu, L. Li, C.-H. Shen, P.-P. Ruan, C.-Y. Liu, L.-W. Ye, *Chem. Eur. J.* **2016**, *22*, 2282; e) L. Hu, C. Chen, Z. Tan, G. Zhu, *Chem. Commun.* **2015**, *51*, 16641; f) S. Sadhukhan, B. Baire, *Adv. Synth. Catal.* **2018**, *360*, 298.
- [10] a) M. M. Aborways, W. J. Moran, *Tetrahedron Lett.* **2014**, *55*, 2127; b) A. Jovtscheff, S. L. Spassov, *Monatsh. Chem.* **1967**, *98*, 2326; c) T. Inokuchi, S. Matsumoto, M. Tsuji, S. Torii, *J. Org. Chem.* **1992**, *57*, 5023; d) S. Sadhukhan, B. Baire, *ChemistrySelect* **2017**, *2*, 8500; e) G. Qiu, Y. Li, L. Ma, H. Zhou, *Org. Chem. Front.* **2017**, *4*, 1069.
- [11] a) M. N. Pennell, M. G. Unthank, P. Turner, T. D. Sheppard, *J. Org. Chem.* **2011**, *76*, 1479; b) M. N. Pennell, P. G. Turner, T. D. Sheppard, *Chem. Eur. J.* **2012**, *18*, 4748; c) M. N. Pennell, M. P. Kyle, S. M. Gibson, L. Male, P. G. Turner, R. S. Grainger, T. D. Sheppard, *Adv. Synth. Catal.* **2016**, *358*, 1519; d) M. N. Pennell, R. W. Foster, P. G. Turner, H. C. Hailes, C. J. Tame, T. D. Sheppard, *Chem. Commun.* **2014**, *50*, 1302; e) E. Barreiro, A. Sanz-Vidal, E. Tan, S.-H. Lau, T. D. Sheppard, S. Díez-González, *Eur. J. Org. Chem.* **2015**, 7544.
- [12] M. Guo, Y. Zheng, J. L. Terell, M. Ad, C. Opoku-Temeng, W. E. Bentley, H. O. Sintim, *Chem. Commun.* **2015**, *51*, 2617.
- [13] *1,3-Dibromoisocyanuric Acid*, S. C. Virgil in *e-EROS Encyclopedia of Reagents for Organic Synthesis* (Ed. P. L. Fuchs), John Wiley & Sons, **2001**.
- [14] a) A. K. Sakkena, P. Mangiaracina, *Tetrahedron Lett.* **1983**, *24*, 273; b) D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3560.

- [15] M. Kuroboshi, T. Ishihara, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1185.
- [16] D. A. Evans, A. H. Horveda, *J. Org. Chem.* **1990**, *55*, 5190.
- [17] A Reaxys® search for acyclic 2,3-dibromo-1,3-diols returned no hits (5th Feb **2018**); The only acyclic *syn*-2,3-dichloro-1,3-diol reported in the literature is the fungal natural product peyrisocoumarin B: Y. Zhao, D. Liu, P. Proksch, S. Yu, W. Lin, *Chem. Biodiversity* **2016**, *13*, 1186.
- [18] a) A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Chem. Commun.* **2005**, 2581; b) D. Obrecht, *Helv. Chim. Acta* **1989**, *72*, 447; c) A. Sniady, K. A. Wheeler, R. Dembinski, *Org. Lett.* **2005**, *7*, 1769; d) A. Sniady, M. S. Morreale, K. A. Wheeler, R. Dembinski, *Eur. J. Org. Chem.* **2008**, 3449; e) A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Eur. J. Org. Chem.* **2006**, 2991.
- [19] R. W. Foster, L. Benhamou, M. J. Porter, D.-K. Bucar, H. C. Hailes, C. J. Tame, T. D. Sheppard, *Chem. Eur. J.* **2015**, *21*, 6107.
- [20] a) A. Padwa, K. R. Crawford, C. S. Straub, S. N. Pieniazek, K. N. Houk, *J. Org. Chem.* **2006**, *71*, 5432; b) R. L. Rae, J. M. Żurek, M. J. Paterson, M. W. P. Bebbington, *Org. Biomol. Chem.* **2013**, *11*, 7946.
- [21] For intermolecular Diels–Alder reactions of 3-halofurans, see: a) A. McCluskey, S. P. Ackland, M. C. Bowyer, M. L. Baldwin, J. Garner, C. C. Walkom, J. A. Sakoff, *Bioorg. Chem.* **2003**, *31*, 68; b) R. N. Ram, N. Kumar, *Tetrahedron Lett.* **2008**, *49*, 799.
- [22] The structure and alkene geometry of **29b** was confirmed by nOe studies and comparison of the observed coupling constants with values obtained from DFT calculations. Please see the supplementary information for further details; see also: A. E. Aliev, D. Courtier-Murias, *J. Phys. Chem. B* **2007**, *111*, 14034.
- [23] For ring expansion of unactivated cyclopropanes via a two-step sequence, see: R. Liu, M. Zhang, G. Winston-McPherson, W. Tang, *Chem. Commun.* **2013**, 49, 4376.
- [24] For direct ring expansion of cyclopropylacetylenes under gold catalysis, see: a) S. Ye, Z.-X. Yu, *Org. Lett.* **2010**, *12*, 804.
- [25] P. Phukan, P. Chakraborty, D. Katakai, *J. Org. Chem.* **2006**, *71*, 7533.

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