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Selectivity in the halohydroxylation of cyclohexadienediols

Ignacio Carrera, Margarita C. Brovetto and Gustavo Seoane*

Departamento de Química Orgánica, Facultad de Química, Universidad de la República, C.C. 1157, Montevideo, Uruguay

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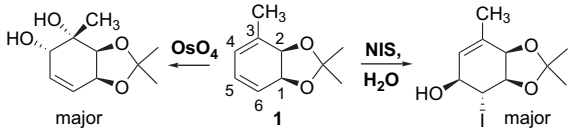
Abstract—The halohydroxylation of a number of cyclohexadienediol derivatives has been investigated. The selectivity of the reaction as a function of the type of substituent on the diene, protecting group of the diol functionality, halonium donor, medium polarity, and temperature is described. Best selectivity is obtained for iodohydrin formation. The course of the reaction for these dienic systems is heavily dependent on steric factors.

1. Introduction

In connection with our ongoing efforts to prepare marine natural products from *cis*-cyclohexadienediols of microbial origin, we have tested a number of electrophilic additions to these dienes. This type of compounds, readily available in our laboratory by biotransformation of substituted benzenes,[1] presents interesting features for the study of these reactions on dienes. The protected cis-diol functionality and the presence of a conjugated dienic system including di- and trisubstituted double bonds allows for the consideration of both the stereo- and regioselectivity of the reactions, respectively. We have previously disclosed the osmylation and the iodohydroxylation of a number of these dienic compounds.[1,2] Both reactions have found repeated application in organic synthesis.[3,4] They are widely used in industrial processes for the synthesis of drugs, pharmaceuticals, agrochemicals, pigments, and photographic materials.[5]

In our dienic system, both reactions showed different (opposite) regioselectivity, whereas the osmylation took place preferentially in the more electron rich double bond of **1**,[1] the iodohydrin was formed exclusively on the disubstituted olefin (Scheme 1).[†,2] Motivated by the difference in selectivity we decided to investigate further the cohalogenation of these dienes, studying mainly the effect of the source of halonium ion and the steric requirements for both regio- and stereoselectivity. In conjugated dienic systems the possibility of 1,2- versus 1,4-addition is another variable to be considered, which has been studied mainly for addition of halogens (particularly in brominations and chlorinations) and electrophilic hydrogen.[6,7–13]



Scheme 1.

For other electrophilic additions, such as oxymercuration[12] and halohydroxylation,[9,14] the volume of available data is more limited. The results of the cohalogenation study for the dienic system and some mechanistic considerations are described here.

2. Results and discussion

2.1. Regioselectivity: effect of the substituents on the diene

The study was started by varying the electronic environment around the dienic system. Thus, the halohydroxylations of electron deficient (**2**, R_1=Br), alkyl substituted (**1** and **3**, R_1=Me and Et, respectively), and electron rich dienes (**4**, R_1=OMe) were studied (Table 1).

There are a number of reports on halohydrin formation for electron deficient dienes such as **2**,[15,16] the attack being always on the more electron rich olefin, following the generalized Markownikoff's rule.

The halohydroxylation was performed using two different halogens, under standard conditions for each one, namely acetyl hypoiodite (Prévost reaction)[17] and/or *N*-iodosuccinimide (NIS)–H_2O for iodine,[18] and *N*-bromosuccinimide (NBS)–H_2O for bromine.[19] The regioselectivity was investigated by considering two parameters: the ratio of electrophilic attack on trisubstituted versus disubstituted olefin,

* Corresponding author. Tel.: +598 2 924 4066; fax: +598 2 924 1906; e-mail: gseoane@fq.edu.uy
† The numbering scheme shown in Scheme 1 for the parent compound is used throughout the text for all compounds.

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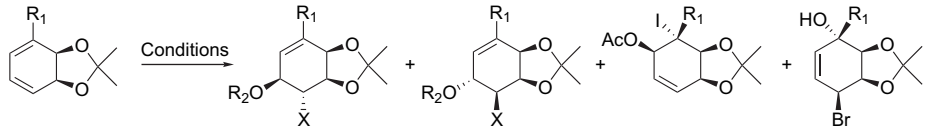
Table 1. Effect of the substituents on the diene



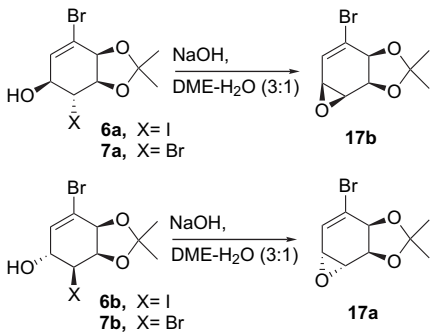
Entry	R_1	Conditions[a]	Time[b] (h)	Product, yield (%)			Tri/di-Olefin[c]	Ratio α/β	1,4- versus 1,2-addition	Overall yield (%)
1	Br	AcOAg, I_2, AcOH	2	**5a**, 89	**5b**, 1		0	89	0	90
2	Br	NIS, DME–H_2O (1:1)	2	**6a**, 75	**6b**, 10		0	7.5	0	85
3	Br	NBS, DME–H_2O (1:1)	2	**7a**, 60	**7b**, 14		0	4.3	0	74
4	Me	AcOAg, I_2, AcOH	1.8	**8a**, 57	**8b**, 3	**9**, 10	0.16	9.6	0	74[d]
5	Me	NIS, DME–H_2O (1:1)	1	**10a**, 79	**10b**, 15		0	5.3	0	94
6	Me	NBS, DME–H_2O (1:1)	1	**11a**, 59	**11b**, 5	**12**, 24	0	2.0	0.37	88
7	Et	AcOAg, I_2, AcOH	2	**13a**, 60	**13b**, 7	**14**, 5	0.07	9.3	0	72
8	Et	NBS, DME–H_2O (1:1)	1.5	**15a**, 52	**15b**, 7	**16**, 16	0	2.4	0.27	75
9	OMe[e]	AcOAg, I_2, AcOH	Aromatization products							
10	OMe[e]	NBS, DME–H_2O (1:1)	Polymerization products							

[a] All reactions were run from 0 °C to rt.
[b] Time for disappearance of starting material (1 mmol). Conversion data points were taken after every 10 min by TLC.
[c] Ratio of addition to trisubstituted versus disubstituted olefin.
[d] Includes 4% of diiodohydrin derivatives, see Table 3.
[e] Used as unprotected diol, because of its unstability toward acetonization.

and the ratio of 1,4- versus 1,2-addition. In addition the stereoselectivity was defined by the ratio of electrophilic attack on the α-face to the attack on the β-face (ratio α/β).

The reaction of compound **2** proceeded in good to excellent yields for both halogens, with exclusive selectivity toward the disubstituted olefin (entries 1–3).

The stereoselectivity was excellent for iodine (entries 1 and 2) and good for bromine (entry 3). The mixture of iodoacetates **5a** and **5b** was very difficult to separate by chromatography, in contrast to the readiness of separation of the iodo- and bromohydrin **6** and **7**. Therefore, the minor stereoisomer **5b** was characterized as the iodohydrin **6b**, after hydrolysis of the acetate and further separation. The regio- and stereochemistry of the products was established by ^1H NMR analysis and, in all cases, the structures were confirmed by base-catalyzed conversion to the known bromoepoxides **17a** and **17b** (Scheme 2).[15b,20]



Scheme 2.

Iodoacetate **5a**, the major product from Prévost reaction on **2**, presented a coupling pattern for H-6 (geminal to the iodine) consisting of a triplet with J 7.8 Hz, suggesting a trans-diaxial relationship with its neighbors. The same type of pattern is observed for all the major stereoisomers of halohydrins, vide infra.

The results were completely different for electron rich dienes (entries 9 and 10). Strongly electron donor groups, namely the methoxyl in **4**, activated the compound in such a way that polymerization and/or aromatization took place. For this system, less active electrophilic donors would be needed in order to obtain the desired addition products.[‡]

For alkyl-substituted dienes such as **1** and **3**, different results were found. In this type of dienes the regioselectivity was complicated by the presence of electrophilic attack on either olefin and also by the competition between 1,2- and 1,4-addition. Prévost reaction of **1** and **3** afforded products resulting from electrophilic attack on either olefin, but 1,4-addition was not observed (entries 4 and 7). Conversely, the reaction of these dienes with NBS–H_2O gave products from 1,2- and 1,4-addition, although electrophilic attack on the trisubstituted olefin was not found (entries 6 and 8). The stereochemistry of the 1,4-addition products, **12** and **16**, indicates that they arise exclusively from β-halonium ions. Also, in agreement with the results for electron deficient dienes of type **2**, better stereoselectivity was obtained for iodine, which gave higher α/β ratios than bromine under

[‡] For diene **4**, all attempts to control the reaction failed, the overoxidation being the main outcome even when reacted with NBS and 1 equiv of H_2O in DME at −10 °C.

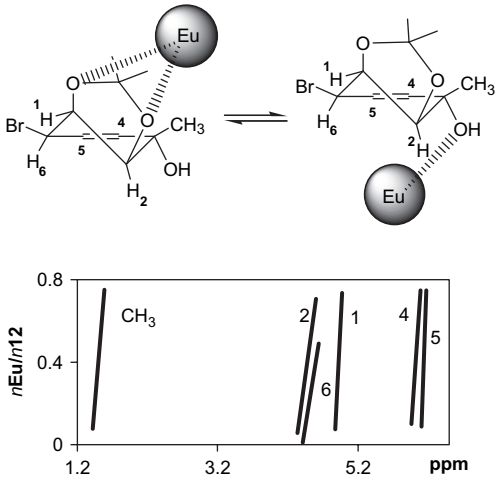
both Prévost and NIS–H_2O conditions (entries 4, 5, and 7 vs 6 and 8). Similar to the electron deficient case, the halohydrins from **1** or **3** with *N*-haloimides were readily separable by column chromatography.

The structures of the products were determined as follows.

For the products resulting from 1,2-addition to the disubstituted olefin (**8**, **10**, **11**, **13**, and **15**), the major diastereomer presented the signal corresponding to the H-6 (geminal to the halogen, at δ 4.00, 4.21, 4.06, 4.03, and 4.05 for **8a**, **10a**, **11a**, **13a**, and **15a**, respectively) as a doublet of doublets, with coupling constants between 6.9 and 9.7 Hz in all the cases, suggesting a trans-diaxial relationship between this proton and their immediate neighbors. In the analogous spectra of the minor isomers the magnitudes of the vicinal couplings associated with the signals due to H-6 (at δ 4.13, 4.08, 4.00, 4.13, and 3.98 for **8b**, **10b**, **11b**, **13b**, and **15b**, respectively) suggest a trans-diaxial arrangement between these protons and H-5 (*J* between 7.4 and 9.3 Hz), together with a cis-relationship to H-1 (*J* between 2.2 and 2.3 Hz). Then, both types of halohydrins correspond to the structures of the known iodohydrins **10a** and **10b**.[2]

The products **9** and **14**, resulting from electrophilic attack on the trisubstituted olefin, presented a noticeable homoallylic coupling between H-1 and H-4 of ^{1-5}J 1.9 Hz, for both cases, which is due to a cis-di-pseudoaxial relationship between these protons, presumably through a twisted-boat conformation.

Regarding the 1,4-addition products (**12** and **16**), the coupling between H-1 and H-6 (*J* 2.0 and 1.9 Hz, respectively) suggests a cis-relationship between them. In addition the tertiary methyl group shows a low enhancement (<1%) in the NOE experiment when one of the methyls from the isopropylidene group is irradiated, thus suggesting a β-disposition for the tertiary methyl group on C-3. To confirm the stereochemistry at C-3, an experiment with NMR shift reagents (using tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato) europium) was performed on **12**. The plot of the molar ratio europium reagent/compound **12** versus chemical shift shown in Scheme 3 presents the progressive deshielding of all the protons on the ring with increasing amounts of shift reagent (higher *n***Eu**/*n***12**). In addition, H-2, H-6, and CH_3 are more sensitive to europium coordination than H-1, H-4, and H-5. This is in agreement with the proposed α stereochemistry for the tertiary alcohol, on the opposite face to the *O*-containing protecting group. If this alcohol was in β-position, the complexation would take place only on this face, and a negligible variation in chemical shifts for H-1, H-2, and H-6 would have been seen (Scheme 3).



Scheme 3.

The observed difference in the product distribution for halohydroxylation of dienes **1** and **3** deserves some comments. There are a number of reports about the dependence of the reactions between dienes and positive halogen donors on the steric requirements of the substrate.[6] Specifically, Dalton found a strong dependence of the regiochemistry and rate of addition on the bulkiness of the substrate,[14,21] and also several authors refer to this point in their work (see Section 2.4).

The ethyl derivative, **3**,[22] was prepared to probe this phenomenon in our dienic system. Then, diene **3** was reacted with acetyl hypoiodite (Prévost) and NBS to give the corresponding cohalogenated products (Table 1, entries 7 and 8).

The yields were comparable, although somewhat lower than those for the methyl substituted diene **1**. The stereoselectivity (ratio α/β) remained unchanged, within the experimental error (entries 7 vs 4 and 8 vs 6). However, the regioselectivity displayed by **3** was higher for the two parameters considered (ratios 1,4/1,2-addition and tri/disubstituted olefin attack). In this context, the relative amount of 1,4-addition product in **3** diminished considerably for bromine. For iodine, it is worth to mention that no 1,4-addition products were observed in the reaction of **1** or **3**. Regarding the 1,4-addition products, the introduction of a bulkier substituent in the dienic system decreased the attack at that position, resulting in a higher ratio. Thus, for diene **1** the β-bromonium ion gave a ratio of 1,2- to 1,4-addition of **11b**–**12**=0.21; diene **3**, in turn, gave a ratio of 1,2- to 1,4-addition more than doubled, **15b**–**16**=0.44.

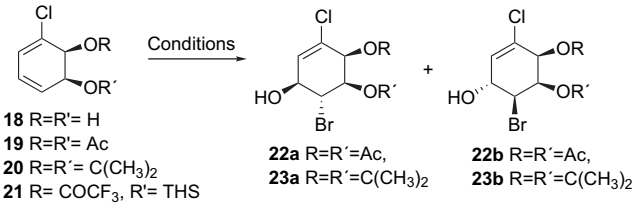
For iodine, although no 1,4-products were detected, a further difference in regioselectivity was observed, depending on the attack on the tri- or disubstituted olefin. Again, ethyl derivative **3** was more selective, since the ratio for the attack on the trisubstituted over the disubstituted olefin, which was 0.16 for **1**, dropped to 0.07 for **3**, representing less than one half of the former value.

It seems that a more crowded steric environment on C-3 retards attack on the trisubstituted olefin (for both 1,2- and 1,4-addition). These findings are in agreement with the proposed strong dependence of the reaction on steric requirements, which makes the preferred site of attack the more accessible, although less electron rich, disubstituted olefin of the dienic system.

2.2. Stereoselectivity: effect of the protecting group

To study the stereoselectivity of the halohydroxylation reaction several dienes with protecting groups of different sizes on the diol functionality were prepared (Table 2). To avoid regioselectivity issues the reactions were performed on

Table 2. Effect of the protecting group



18 R=R'= H
19 R=R'= Ac
20 R=R´= $C(CH_3)_2$
21 R= $COCF_3$, R'= THS

22a R=R´=Ac, **23a** R=R´=$C(CH_3)_2$ — **22b** R=R´=Ac, **23b** R=R´=$C(CH_3)_2$

Entry	Protecting groups	Conditions[a]	Product, yield (%)		Ratio α/β	Overall yield (%)
1	R=R′=Ac	NBS, acetone–H_2O (4:1)	**22a**, 54	**22b**, 21	2.6	75
2	R, R′=$C(CH_3)_2$	NBS, DME–H_2O (1:1)	**23a**, 48	**23b**, 7	6.9	55
3	R=$COCF_3$, R′=THS	NBS, DME–H_2O (1:1)	Decomposition[b]			

[a] All reactions were run from 0 °C to rt.
[b] Decomposition products with losses of the protecting groups.

derivatives of chlorocyclohexadienediol **18**,[23] an electron deficient diene analogous to **2**.

The easily prepared diacetate **19**[2] gave low yields of bromohydrins (less than 35%) when treated with NBS in DME–H_2O and, therefore, several different solvent systems were tried. Best results were obtained in acetone–H_2O (4:1), yielding a ratio α/β=2.6 with an overall yield of 75%. This low stereoselectivity was greatly improved by using the bulkier isopropylidene group in **20**,[24a] with the former solvent system, which afforded a ratio α/β=6.9 in 55% yield (Table 2, entry 2).[24b]

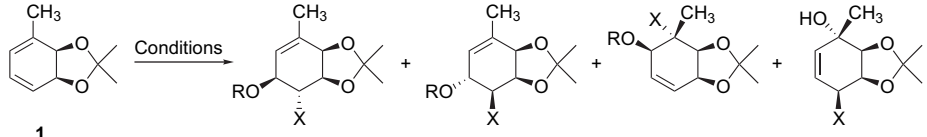
Finally, the differently protected compound **21**[25a] decomposed under the reaction conditions, presumably via NBS-mediated oxidation of the silylated protecting group.[25b] From these results, we decided to carry out further reactions using the large isopropylidene protecting group.

2.3. Effect of the halonium source

To complete the study on the effect of the halonium source, the reaction of diene **1** with *N*-chlorosuccinimide (NCS) was also tried, in addition to the other *N*-halosuccinimides and the Prévost reaction. All of them are presented in Table 3, for comparison. In all cases studied the halonium ion formation preferentially occurred on the α-face, with the exception of the reaction of chlorohydrin formation, which gave roughly equal amounts of products resulting from α- and β-chloronium ions (entry 4, Table 3). The ratio α/β increased with the size of the halogen considered, reaching preparatively useful values (greater than 4) for the iodine atom (entries 1 and 2, Table 3). On the other hand, the ratio of 1,4- to 1,2-addition increased significantly from the iodohydrins, where no 1,4-addition products were detected, to bromo- and chlorohydrin (0.37 and 1.0, respectively, entries 3 and 4, Table 3). The stereochemistry of the 1,4-addition products (**12** and **25**) indicates that they arise exclusively from β-halonium ions. This preference is more noticeable in chlorohydrins: all of the products derived from the β-chloronium ion correspond to 1,4-addition (**25**, entry 4, Table 3). For the case of bromohydrins, in turn, the 1,4-addition product, **12**, represents 82% of the products arising from the β-bromonium ion (**11b** and **12**), and finally both methods of iodohydrin formation did not afford any 1,4-addition products. Again, the most selective halogen is the iodine, giving high preference for α-halonium ions.

The yields of bromo- and iodohydroxylation were good to excellent; conversely, the chlorohydroxylation gave a disappointing 30% yield after disappearance of starting diene, together with aromatization products.

Table 3. Effect of the halonium source



1

8a R= Ac, X= I
10a R= H, X= I
11a R= H, X= Br
24a R= H, X= Cl

8b R= Ac, X= I
10b R= H, X= I
11b R= H, X= Br

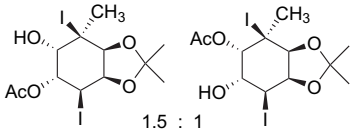
9 R= Ac, X= I

12 X= Br
25 X= Cl

Entry	Conditions[a]	Time[b] (h)	Product, yield (%)					Ratio α/β	1,4- Versus 1,2-addition	Overall yield (%)
1	AcOAg, I_2, AcOH	1.8	**8a**, 57	**8b**, 3	**9**, 10	—	**26**, 4[c]	9.6	0	74
2	NIS, DME–H_2O (1:1)	1	**10a**, 79	**10b**, 15	—	—	—	5.3	0	94
3	NBS, DME–H_2O (1:1)	1	**11a**, 59	**11b**, 5	—	**12**, 24	—	2.0	0.37	88
4	NCS, DME–H_2O (1:1)	40	**24a**, 15	—	—	**25**, 15	—	1.0	1.0	30

[a] All reactions were run from 0 °C to rt.
[b] Time for disappearance of starting material.
[c] Mixture of monoacetates from dihalohydrins, see Scheme 4.

It is interesting to note that when the iodohydroxylation was performed with acetyl hypoiodite (Prévost reaction) another product was observed, **26**, isolated as an inseparable 1.5:1 mixture of monoacetates (Scheme 4). This product resulted from electrophilic attack on both double bonds, always through the corresponding β-iodonium ion. The regiochemistry obtained can be rationalized invoking, for the second attack, an anchimeric assistance of the allylic pseudoequatorial acetate introduced in the first attack, in a similar way as reported by Sweeney for iodohydrin formation on acyloxycyclohexenes.[26] The order of events is not relevant to the final stereochemistry, giving the same mixture of monoacetates **26**. However, according to the isolated products resulting from mono-iodohydroxylation, it seems likely that the first step was the formation of iodoacetate **8b**, and further attack afforded **26**.



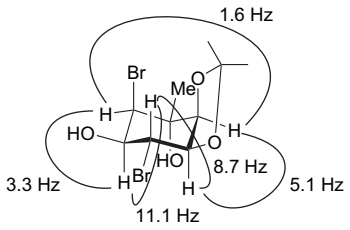
26

Scheme 4.

Next, the effect of the temperature over the reaction of *N*-haloimides on diene **1** was studied, performing the iodo- and bromohydroxylation at −30, 0, and 50 °C.

Within the experimental error the product distribution, determined by integration of the ^{1}H NMR signals in the mixtures of reaction, did not vary with temperature. Also, to study the behavior toward equilibration, one of the mixtures of reaction, corresponding to entry 3, Table 3, was left reacting overnight once the starting material had disappeared, the starting product ratio being **11a**–**11b**–**12**=67:6:27, as determined by ^{1}H NMR. In this event, a new product was observed, which was identified as a dibromohydrin, **27**. The final ratio of products was **11a**–**11b**–**12**–**27**=59:6:27:8, suggesting that the new product resulted exclusively from reaction of bromohydrin **11a** and no equilibration occurred. To confirm this further, major bromohydrin **11a** was isolated and subjected to the same reaction conditions overnight. Neither compound **12** nor **11b** was detected, thus confirming the absence of equilibration among bromohydrins under these conditions. The spectroscopic data of dibromohydrin **27** were in full accord with the proposed structure. The magnitudes of the observed coupling between H-6 and its immediate neighbors ($J_{6,1}$ 8.7 Hz and $J_{6,5}$ 11.1 Hz) suggest a trans-diaxial relationship between this proton and H-1 and H-5. A long distance coupling between H-2 and H-4 (^{1-4}J 1.6 Hz) is suggestive of a cis-diequatorial arrangement on a cyclohexane ring (Scheme 5). The formation of product **27** can be rationalized through a second electrophilic attack on the major product, **11a**, producing a β-bromonium ion that opens to afford the Markownikoff's product.

The effect of modifying the solvent polarity was also investigated, by changing the amount of H_2O in mixtures DME–H_2O. Data for the reaction of diene **1** with NBS or NIS in mixtures of DME and decreasing amounts of water are presented in Table 4.



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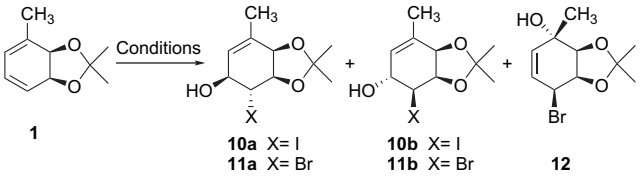
Scheme 5.

Table 4. Effect of the medium polarity



1 **10a** X= I, **11a** X= Br **10b** X= I, **11b** X= Br **12**

Entry	Conditions[a]	H_2O (equiv)/ **1** (equiv)	Product, ratio[b]
1[c]	NIS, 1:1 DME–H_2O	140	**10a**, 84 **10b**, 16 —
2[c]	NIS, 25:1 DME–H_2O	10	**10a**, 92 **10b**, 8 —
3[c]	NIS, 140:1 DME–H_2O	2	**10a**, 97 **10b**, 3 —
4	NBS, 1:1 DME–H_2O	140	**11a**, 64 **11b**, 6 **12**, 30
5	NBS, 5:1 DME–H_2O	50	**11a**, 67 **11b**, 7 **12**, 26
6	NBS, 25:1 DME–H_2O	10	**11a**, 69 **11b**, 6 **12**, 25

[a] All reactions were run in 5 mL of DME–H_2O as specified, from 0 °C to rt.
[b] Determined by integration of ^{1}H NMR signals in the reaction mixture.
[c] From Ref. 2.

As previously reported,[2] the stereoselectivity of the iodohydroxylation showed a modest enhancement for the α-attack with decreasing amounts of water, which could be ascribed to the diminished polarity of the solvent system. For the bromohydroxylation, however, the data are not conclusive, showing a slight variation in the same sense, although within the experimental error. Regarding the regioselectivity, the change in the ratio of 1,4- to 1,2-addition is small, within the experimental error.

2.4. Mechanistic considerations

The results presented herein indicate that halohydroxylation of substituted cyclohexadienediols proceeds with variable selectivity.

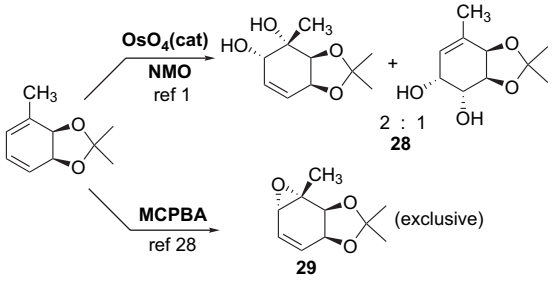
The selectivity of alkene additions using electrophilic halogen donors depends on a number of factors including, in addition to the structure of reactants and nature of the solvent, the bridged or unbridged structure of the intermediate halonium ion, its association with nucleophilic partners, and its lifetime.[27,6] The controversial question about the equilibrium between bridged and unbridged structures of the ionic intermediates is further complicated in conjugated dienes by the possibility of resonance and extensive charge delocalization into the second double bond, thus allowing the competition between 1,2- and 1,4-addition and also between each particular double bond for addition.

Regarding the cyclohexadienediols, there is a clear-cut difference between the additions to electron deficient dienes such as **2**, **19**, and **20**, and to alkyl-substituted ones, namely

1 and **3**. For dienes **2**, **19**, and **20** the addition took place exclusively on the disubstituted and more electron rich olefin. This behavior was also observed for other electrophilic reactions, such as osmylations, thus suggesting that the halogeno-olefin is too deactivated to undergo this type of additions.[1] For epoxidations, the use of peroxyacids produced exclusively the disubstituted epoxide,[28,29] but stronger conditions using permanganate ions result in attack on the entire dienic system (possibly through a cyclic 1,4 intermediate).[30]

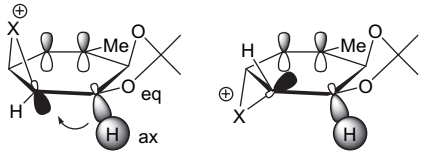
On the other hand, dienes **1** and **3** show a more complicated behavior toward electrophilic additions. The formal HOX addition afforded products resulting from attack on one or both olefins. Reactions of NIS–H_2O, NBS–H_2O, and NCS–H_2O with dienes **1** and **3** gave addition products derived from initial electrophilic attack exclusively on the disubstituted, less electron rich, double bond. The reaction under Prévost conditions, however, produced a mixture of products resulting from attack on both double bonds. This reaction is, therefore, regiochemically less selective than the corresponding iodohydroxylation using NIS.

The regiochemical outcome of the electrophilic additions using *N*-halosuccinimides is different from other related additions, namely osmylation and peroxyacid epoxidation. In these latter reactions the electrophilic attack on diene **1** took place mainly on the trisubstituted, more electron rich, olefin, giving products **28** and **29** (Scheme 6).[1,28] Clearly, there are differences between these electrophilic additions and the formal addition of HOX to olefins. Some of them will be discussed below.



Scheme 6.

Our system also presents allylic substitution, which adds another parameter to be considered for the selectivity. The regio- and stereochemistry of electrophilic addition to allylic double bonds has been modeled by Kahn et al. some years ago.[31] Those models indicate, for allylic hydroxy or alkoxy substituent, a preference for the addition of the electrophile *syn* to the substituent, which is based on electrostatic arguments.[32] This selectivity for the *syn* adduct was recently rationalized by Ganem et al.,[33] mentioning that, for 1,2-addition of HOX to alkenes, an additional stabilization of the intermediate *syn*-halonium ion might be obtained through a hyperconjugative generalized anomeric effect.[34] In this case, if the polar allylic substituent is oriented in pseudoequatorial position, the corresponding pseudoaxial allylic C–H σ-bond can serve as an electron releasing group to stabilize the electronegative halonium ion by back-donation into the C–X σ*-bond. This effect would be more pronounced in the formation of the more electronegative chloronium ion. For cyclohexene-derived *syn*-halonium ions, molecular models indicate a good antiperiplanar orbital overlap between the C–H and C–X σ*-bonds (Scheme 7). The preference for the pseudoequatorial disposition of the allylic substituent during halohydrin formation in acyloxycyclohexenes was recently mentioned.[26]



Scheme 7.

In the reaction of dienes such as **1** and **3** with *N*-halosuccinimides, a preference for the formation of products resulting from the α-halonium ion is observed, which increases with the size of the halogen atom (ratio α/β, Tables 1 and 3). Considering the steric crowding given by the acetonide on the β-face of the dienic system, this selectivity in reactions involving the attack of bulky halogen ions is expected. What is surprising, however, is the low values obtained for the ratio of α/β products in the chloro- and bromohydrin cases. It seems that other factors are involved, including the generalized anomeric effect. This effect, that favors β-halonium ions, is stronger for the more electronegative halogen atoms and may account for the diminished selectivity found for these two halogens.

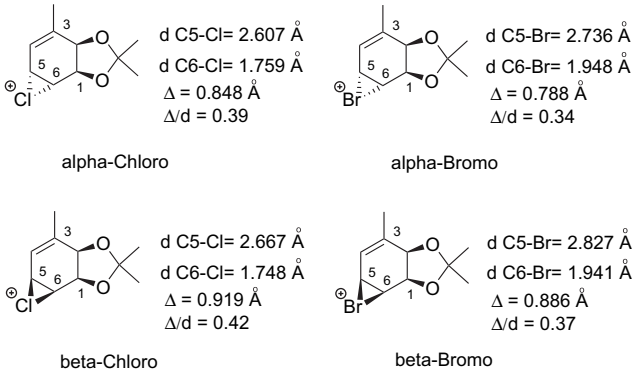
The dependence of electrophilic additions on steric effects is related to the nature of the incoming electrophile and the structure of the transition state. Thus, whereas the brominations are independent of the steric effects (higher rates in more highly substituted olefins),[12] the sensitivity of halohydroxylations to steric effects is well documented.[9,14,21,35] For unsymmetrical dienes, in particular, a large influence of the steric factor was described by Dalton, affecting the rate and the selectivity (regiochemistry) of addition.[14,21]

The halohydroxylation of dienes **1** and **3** proved to be highly dependent on steric factors, which made the products resulting from α-halonium ions to predominate (Tables 1 and 3). In addition to this effect on the stereoselectivity, the replacement of the methyl group on C-3 of diene **1** for the ethyl group in diene **3** enhanced the regioselectivity of the reaction (Table 1). The bulkier ethyl group effectively retarded the attack (both electrophilic and nucleophilic) on the trisubstituted olefin, producing higher preference for reaction at the disubstituted olefin and slower overall reaction rates (Table 1, entries 4–8). As expected, the ratio α/β did not change, within the experimental error, when passing from **1** to **3** (Table 1, entries 4–8).

In the theoretical model developed by Kahn for electrophilic additions,[31] the experimental results for osmium tetroxide dihydroxylation and peroxyacid epoxidation of allylic ethers showed discrepancies with the proposed model (i.e., the major addition product is not *syn* to the allylic substituent). For dienes **1** and **3**, we also obtain differences in the selectivity, but this time related specifically to the regiochemistry of addition. The preference of osmium tetroxide and peroxyacids to attack the more electron rich olefin of diene **1**, which is

opposite to that for halohydroxylations, points out the difference between the operating mechanisms and seems to indicate that the former reactions are closer to brominations, where steric factors are less important due to a reactant-like transition state.[12]

Another point deserving attention is the 1,2- versus 1,4-addition in the dienic system. Regardless of the existence of a bridged or unbridged ion, the actual intermediate would be more reactive with a better overlap of the orbitals involved, namely the C–X bond and the π cloud of the vicinal double bond. Inspection of molecular models of our dienic system indicates that the geometrical requirements for a good overlap are more easily met when the halonium ion is on the β-face. In this arrangement, better overlap is obtained for the β-halonium ion with both the neighbor olefin and the vicinal pseudoaxial C–H (generalized anomeric effect), through a twisted-boat conformation (see Scheme 7). This qualitative picture agrees with preliminary theoretical calculations, performed at semiempirical level using the AM1 Hamiltonian.[36] The structures of α- and β-halonium ions were modeled for the bromonium and chloronium cases, using semiempirical methods. The reliability of the data obtained using this type of methods is moderate, but the information is easily obtained and is useful to indicate qualitative trends, which was the purpose for its use. The calculations showed a large difference between the bond distances of the C–X bonds for each particular halonium ion, being longer for the C–X bond next to the double bond (Scheme 8).



Scheme 8.

Because of dispersal of charge in the allylic system, the bond between the halogen and C-5 is weakened so that an unsymmetrical intermediate is formed. The relative difference between the C–X bonds for each structure is given by the Δ/*d* parameter, which takes into account the different size of the halogens. This parameter indicates that the chloronium is the more unsymmetrical ion, suggesting a higher delocalization of charge. This is more noticeable for the β-halonium ions, in which both halogens display higher values. Then, these results are in agreement with the fact that bridged halonium ions are better supported by halogen atoms following the order iodine>bromine>chlorine,[37] and also indicate that bridging is less effective (producing more charge dispersal) for the β-halonium ions.

The experimental results seem to agree with this description. For the three halogens studied, the 1,4-addition products were derived exclusively from the β-halonium ions, the α-ions giving only 1,2-addition. The more delocalized chloronium gives the highest ratio of 1,4-addition products, followed by bromine, and iodine does not give 1,4-addition products (Table 3). The exclusive 1,2-addition resulting from α-halonium ions (Table 1, entries 4–8, and Table 3) could be explained by a minimum delocalization of charge and the absence of S_N2' due to deficient overlap (and also due to the steric hindrance of the β-face, in case of *anti* attack).

In all the cases of 1,4-addition, the nucleophilic attack on C-3 is always α, suggesting an effective shielding of the β-face by the protecting group or an *anti* attack on the β-halonium ion through an S_N2' reaction.

Another observation is related to the difference in the mode of attack on dienes **1** and **3** to give 1,2-addition products when using Prévost or NXS–H_2O conditions. The regioselectivity of the Prévost reaction is intermediate between the NXS-mediated halohydroxylations and other electrophilic additions (osmylations and epoxidations), giving minor products resulting from attack on the more electron rich trisubstituted olefin. Also, there is a dependence on the steric environment of the olefin, since the attack on the more hindered trisubstituted olefin of diene **3** represents less than one half of the attack on the corresponding olefin in **1** (Table 1, entries 7 vs 4). Undoubtedly, several factors influence the mechanism of formation and collapse of the halonium ions and, therefore, determine the regiochemical ratios of products. Such factors may involve differences in the association state and bridging of the halonium ions and differences in anion structures and reactivities.[27,31,38] These factors play different roles in both types of halohydroxylations.

In addition, in an attempt to better understand the parameters affecting the selectivity in this dienic system, some reactions were performed at different temperatures and in solvent mixtures of different polarities.

All conditions tried involved polar media, although of variable polarity ranging from aqueous mixtures (mainly with DME) to AcOH. The data from Table 4 show that for NBS- and NIS-mediated halohydroxylations in polar media, the polarity of the solvent may vary significatively without causing major changes in the product distribution. The effect could be analyzed taking into account two factors, the stereo- and the regioselectivity of attack. The stereoselectivity is dependent primarily on the degree of dissociation of the incoming electrophile and the possibility of interaction with the directing group. The dissociation of the electrophile is related to the polarity of the medium, which governs its effective size, and thus a less polar system favors the electrophilic attack from the less hindered α-face. Although satisfactory for the reaction of NIS (Table 4, entries 1–3), the dependence of the electrophile's size with polarity cannot explain alone the small variation observed for NBS (Table 4, entries 4–6). In this latter case, the solvent may influence another feature of the system, namely the relative stability of the isomeric halonium ions via the anomeric effect. The polarity affects the magnitude of the anomeric effect, which is more noticeable for the more polar halonium

ion (bromonium) in low polarity media,[34a] thus favoring the β-bromonium ion with decreasing polarity. For the bromohydroxylation, then, the effect of polarity on the electrophile's size (higher α/β ratio with decreasing polarity) is counter balanced by its effect on the stability of the β-bromonium ion, favoring the attack on the β-face with diminished polarity. The overall result of these opposite trends is a small variation in the α/β ratio (Table 4, entries 4–6). Regarding the regioselectivity, our data are in agreement with the proposed no dependence of bridging with the polarity of the solvent.[6,27]

The effect of the temperature on NBS- and NIS-mediated halohydroxylations indicates that the temperature does not influence the product distribution within the range −30 to 50 °C.

Finally, the data obtained in this study seem to suggest that the halohydroxylations of cyclohexadienediols follow a reaction path including an irreversible electrophilic attack on form the halonium ion, which is determined by the relative stability of these ions. In these systems, the steric factors are predominant, conferring greater stability to the α-halonium ion (less crowded) over the corresponding β-isomer (more crowded, although stabilized by anomeric effect). The interplay between steric and stereoelectronic factors, among others, determines the relative stability of intermediate species and, therefore, the final product distribution. If the halonium ions were formed reversibly, the product distribution in formal HOX additions would be determined not by the thermodynamically more stable ion, but by the rate of opening of this intermediate, as pointed out by several authors.[26,31,32d,33] For our cyclohexadienediol system, this would imply a higher selectivity for the β-product, resulting from a faster α-nucleophilic opening of the β-halonium ion, which is favored based on steric grounds. The experimental results show an opposite selectivity for all cases, in agreement with an irreversible formation of the halonium ion. The sensitivity to the steric requirements seems to be consistent with a product-like transition state, as opposed to other related electrophilic additions, such as brominations.

In summary several considerations on the mechanism of the halohydroxylations of cyclohexadienediol derivatives emerge:

(i) The selectivity of the reaction is determined primarily by the steric requirements of the reactants. All reactions showed a marked preference for products derived from α-halonium ions, except in the reaction with NCS where equal amounts of α- and β-product are obtained. For alkyl-substituted dienes, the steric effects also influence the ratio of disubstituted versus trisubstituted olefin attack, retarding the attack on the more crowded double bond.

(ii) The ratio of 1,4- versus 1,2-addition follows an inverse relationship to the bridging ability of the halonium ions: the most bridged iodonium ions do not afford 1,4-addition products, whereas chloronium ions give roughly the same amounts of each addition mode. All 1,4-addition products were derived from β-halonium ions, which are the isomers exhibiting best overlap and charge dispersal with the vicinal olefin, according to preliminary calculations. In addition, the nucleophilic attack on the intermediate halonium ion is always α, in agreement with an ion with charge dispersal in the allylic system and a hindered β-face, thus favoring an α-nucleophilic attack. A less hindered *anti* nucleophilic opening of a bridged β-halonium ion, via an S_N2' mechanism, cannot be ruled out, although this is less likely since it would imply greater proportion of this mechanism in chloronium (and also bromonium) ions, which are those with lower bridging ability. The behavior of *N*-haloimide-mediated halohydroxylations in different solvents is in agreement with the proposed no dependence of bridging with solvent variations.

(iii) Steric and stereoelectronic effects play different roles in these reactions when compared to related electrophilic additions, such as epoxidation and osmylations (and also brominations[12]). The *N*-haloimide-mediated halohydroxylations are highly dependent on steric requirements (precluding the attack on the more hindered, although more electron rich olefin) whereas in the related additions the preferential attack is on the more alkyl-substituted olefin. The Prévost reaction, in turn, shows an intermediate behavior, being more stereoselective but less regioselective than the corresponding NIS-mediated iodohydroxylation.

3. Conclusion

The halohydroxylations of cyclohexadienediol derivatives have been investigated using different conditions and halonium sources. The importance of the steric factors in the course of the reaction is highlighted. Best overall selectivity is achieved using iodine, although bromine is also synthetically useful, especially in deactivated systems. On the other hand, for the chlorine case the reaction was neither selective nor efficient, unsuitable for preparative purposes. Strongly activated systems (enol ethers) require less active electrophilic halogen donors in order for the reaction to be useful under standard conditions. Investigations in this area are in progress and will be disclosed in due course.

4. Experimental

4.1. General techniques

All non-hydrolytic reactions were carried out in a nitrogen atmosphere with standard techniques for the exclusion of air. All solvents were distilled prior to use. Melting points were determined on a Gallenkamp capillary melting point apparatus and are uncorrected. Mass spectra were recorded on a Shimadzu GC–MS QP 1100 EX instrument using the electron impact mode (70 or 20 eV). Infrared spectra were recorded either on neat samples (KBr disks) or in solution on Perkin–Elmer 1310 or Shimadzu FT-IR 8101A spectrometers. NMR spectra were obtained in $CDCl_3$ on a Bruker Avance DPX-400 instrument. Proton chemical shifts (δ) are reported in parts per million downfield from TMS as an internal reference, and carbon chemical shifts are reported in parts per million relative to the centerline of the $CDCl_3$ triplet (77.0 ppm). Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA, USA, or determined on a Fisions EA 1108 CHNS-O microanalyzer.

Optical rotations were measured on a Zuzi 412 polarimeter using a 0.5 dm cell. $[\alpha]_D$ values are given in units of deg cm^2/g and concentration values are expressed in g/100 mL. Diols **1**–**4**, and **18** were obtained by fermentation of the corresponding arenes. Analytical TLC was performed on silica gel 60 F_{254} plates and visualized with UV light (254 nm) and/or *p*-anisaldehyde in acidic ethanolic solution. Flash column chromatography was performed using silica gel (Kieselgel 60, EM reagent, 230–400 mesh).

4.2. General procedure for Prévost reaction

To a stirred solution of cyclohexadienediol acetonide (1.9 mmol) and silver acetate (657 mg, 3.9 mmol) in acetic acid (20 mL) was added iodine (500 mg, 1.9 mmol) in small lots for 3 h. The mixture was protected from light and stirred at ambient temperature for 3 h. The precipitated silver iodide was filtered off; the filtrate was diluted with CH_2Cl_2 (50 mL), neutralized with saturated aqueous $NaHCO_3$ (2×30 mL), washed with water (2×30 mL), 20% aqueous solution of $NaHSO_3$ (2×30 mL,), again with water (2× 30 mL), and dried over Na_2SO_4. After filtration of the solids, solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel using hexanes–ethyl acetate as eluant.

4.3. General procedure for halohydrin preparation with NXS in DME–H_2O

To a 0 °C stirred solution of cyclohexadienediol acetonide (1.9 mmol) dissolved in the corresponding mixture of DME–H_2O (5 mL/mmol of alkene) was added 1.1 equiv of NXS. The mixture protected from light was stirred and let to warm up to ambient temperature. After the specified time, it was diluted with saturated solution of $NaHSO_3$ and extracted with methylene chloride. The combined organic layers were washed with saturated NaCl, dried over $MgSO_4$, and then the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel using hexanes–ethyl acetate as eluant.

4.3.1. (1*R*,2*S*,5*S*,6*S*)-3-Bromo-6-iodo-1,2-isopropylidenecyclohex-3-ene-5-yl acetate (5a). Yellow crystalline solid; mp 112.0–113.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 3H), 1.54 (s, 3H), 2.14 (s, 3H), 4.16 (t, 1H, *J* 7.8 Hz), 4.61 (dd, 1H, *J* 5.6, 7.9 Hz), 4.66 (d, 1H, *J* 5.6 Hz), 5.57 (dd, 1H, *J* 3.0, 7.5 Hz), 6.22 (d, 1H, *J* 3.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2 (CH_3), 26.5 (HC–I), 26.6 (CH_3), 28.4 (CH_3), 73.2 (HC–O), 76.8 (HC–O), 79.4 (HC–O), 112.2 (C), 123.8 (C), 130.8 (=CH), 170.2 (C=O); IR ν_{max} (KBr)/cm^{-1}: 2924, 2851, 1740, 1373, 1265, 738; EIMS *m*/*z* (%): 416–418 (2, M^+), 401–403 (77, M^+-CH_3), 299–301 (54, $M^+-OAc-C_3H_6O$), 189–191 (38, $M^+-OAc-C_3H_6-I$), 172–174 (60, $M^+-OAc-C_3H_6O-I$), 127 (8, I^+), 81 (5, Br^+), 43 (100, Ac^+); $[\alpha]_D^{25}$ +58.4 (*c* 1.5, $CHCl_3$).

4.3.2. (1*R*,2*S*,5*R*,6*R*)-3-Bromo-6-iodo-1,2-isopropylidenecyclohex-3-ene-5-yl acetate (5b). Characterized as its unprotected iodohydrin **6b**.

4.3.3. (1*R*,2*S*,5*S*,6*R*)-3-Bromo-6-iodo-1,2-*O*-isopropylidenecyclohex-3-ene-1,2,5-triol (6a). White solid, mp 71.3–72.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 3H), 1.53 (s, 3H), 3.04 (br s, 1H), 4.36 (dd, 1H, *J* 4.0, 4.3 Hz), 4.40 (t, 1H, *J* 4.3 Hz), 4.70 (m, 2H), 6.39 (d, 1H, *J* 4.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.3 (HC–I), 26.9 (CH_3), 28.4 (CH_3), 72.4 (HC–O), 76.9 (HC–O), 79.9 (HC–O), 112.6 (C), 124.7 (C), 131.3 (CH=); IR ν_{max} (KBr)/cm^{-1}: 3400 (br), 2986, 2932, 1641, 1221, 1157, 1062, 1007, 866; EIMS *m*/*z* (%): 361–359 (100, M^+-CH_3), 301–299 (47, $M^+-C_3H_6O_2$), 220 (13, $M^+-C_3H_6O_2-Br$), 191–189 (21, $M^+-C_3H_7O-I$), 174–172 (95, $M^+-C_3H_6O_2-I$), 110 (65, $M^+-C_3H_7O-I-Br$), 81 (100, Br^+), 59 (88, C_3H_7O); $[\alpha]_D^{25}$ +20 (*c* 0.44, CH_2Cl_2). Anal. required for $C_9H_{12}O_3BrI$: C, 28.83; H, 3.23%. Found: C, 29.10; H, 3.35%.

4.3.4. (1*R*,2*S*,5*R*,6*S*)-3-Bromo-6-iodo-1,2-*O*-isopropylidenecyclohex-3-ene-1,2,5-triol (6b). White solid, mp 75.4–76.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 3H), 1.45 (s, 3H), 3.07 (br s, 1H), 4.12 (dd, 1H, *J* 2.2, 9.3 Hz), 4.53 (td, 1H, *J* 1.8, 9.2 Hz), 4.56 (dd, 1H, *J* 1.7, 5.0 Hz), 4.71 (m, 1H), 6.28 (d, 1H, *J* 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.7 (CH_3), 27.7 (CH_3), 32.0 (HC–I), 71.4 (HC–O), 77.2 (HC–O), 79.6 (HC–O), 110.0 (C), 124.5 (C), 132.7 (CH=); IR ν_{max} (KBr)/cm^{-1}: 3400 (br), 1258, 1138, 1096, 1043, 932, 866, 822, 737; EIMS *m*/*z* (%): 361–359 (13, M^+-CH_3), 191–189 (50, $M^+-C_3H_7O-I$), 174–172 (49, $M^+-C_3H_6O_2-I$), 110 (100, $M^+-C_3H_7O-I-Br$), 127 (31, I^+), 81 (34, Br^+), 59 (52, C_3H_7O); $[\alpha]_D^{25}$ −31 (*c* 0.72, CH_2Cl_2). Anal. required for $C_9H_{12}O_3BrI$: C, 28.83; H, 3.23%. Found: C, 29.14, H, 3.43%.

4.3.5. (1*R*,2*S*,5*S*,6*R*)-3,6-Dibromo-1,2-*O*-isopropylidenecyclohex-3-ene-1,2,5-triol (7a).[16a] White crystalline solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.37 (d, 1H, *J* 4.8 Hz), 4.69 (m, 1H), 4.62 (m, 1H), 4.29 (m, 2H), 2.99 (br s, 1H), 1.55 (s, 3H), 1.44 (s, 3H).

4.3.6. (1*R*,2*S*,5*S*,6*R*)-3,6-Dibromo-1,2-*O*-isopropylidenecyclohex-3-ene-1,2,5-triol (7b). White crystalline solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.27 (d, 1H, *J* 1.8 Hz), 4.63 (m, 2H), 4.57 (m, 1H), 4.04 (m, 1H), 2.99 (br s, 1H), 1.46 (s, 3H), 1.28 (s, 3H). Characterized by conversion to known epoxide **17a**.

4.3.7. (1*R*,2*R*,5*S*,6*R*)-6-Iodo-1,2-*O*-isopropylidene-3-methylcyclohex-3-ene-5-yl acetate (8a). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 3H), 1.48 (s, 3H), 1.85 (s, 3H), 2.12 (s, 3H), 4.00 (dd, 1H, *J* 9.5 Hz), 4.35 (d, 1H, *J* 5.8 Hz), 4.48 (dd, 1H, *J* 5.8 Hz), 5.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.6 (CH_3), 21.4 (CH_3), 26.4 (CH_3), 27.9 (CH_3), 31.5 (HC–I), 73.5 (HC–O), 75.5 (HC–O), 79.4 (HC–O), 110.9 (C), 125.6 (HC=), 170.3 (C=O); IR ν_{max} (KBr)/cm^{-1}: 2986, 2856, 1746, 1372, 1233, 1219, 1161, 1026, 970, 876; EIMS *m*/*z* (%): 211 (36, M^+-CH_3-I), 168 (7, $M^+-C_3H_6O-I$), 151 (2, $M^+-C_3H_6O_2-I$), 109 (100, $M^+-C_3H_6O-I-OAc$); $[\alpha]_D^{20}$ 0.6 (*c* 1.02, CH_2Cl_2). Anal. required for $C_{12}H_{17}O_4I$: C, 40.90; H, 4.82%. Found: C, 41.62; H, 4.95%.

4.3.8. (1*R*,2*R*,5*R*,6*S*)-6-Iodo-1,2-*O*-isopropylidene-3-methylcyclohex-3-ene-5-yl acetate (8b). Characterized as its unprotected iodohydrin **10b**.

4.3.9. (1*S*,2*S*,3*R*,4*R*)-3-Iodo-1,2-*O*-isopropylidene-3-methylcyclohex-5-ene-4-yl acetate (9). Yellow oil; ^{1}H

NMR (400 MHz, $CDCl_3$): δ 1.39 (s, H), 4.2 (d, 1H, *J* 5.2 Hz), 4.68 (m, 1H), 5.40 (dd, 1H, *J* 1.9, 3.5 Hz), 5.6 (m, 1H), 5.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4 (CH_3), 24.4 (CH_3), 26.9 (CH_3), 28.2 (CH_3), 72.8 (HC–O), 72.8 (C), 73.3 (HC–O), 79.9 (HC–O), 110.2 (C), 126.1 (HC═), 129.4 (HC═); 170.6 (C═O); IR ν_{max} (KBr)/cm^{-1}: 3040, 2988, 2882, 1747, 1373, 1244, 518; EIMS *m/z* (%): 227 (37, M^+-I), 169 (12, $M^+-C_3H_6O$–I), 167 (3, M^+-AcOH–I), 141 (18), 127 (4, I^+), 125 (100), 59 (9, AcO); $[\alpha]_D^{20}$ 92 (*c* 0.3, CH_2Cl_2).

4.3.10. (1*R*,2*R*,5*S*,6*R*)-6-Iodo-1,2-*O*-isopropylidene-3-methylcyclohex-3-ene-1,2,5-triol (10a). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 3H), 1.47 (s, 3H), 1.86 (s, 3H), 2.77 (br s, 1H), 4.21 (t, 1H, *J* 6.9 Hz), 4.31 (m, 1H), 4.42 (d, 1H, *J* 5.2 Hz), 4.56 (dd, 1H, *J* 5.5, 7.4 Hz), 5.70 (d, 1H, *J* 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.2 (CH_3), 26.7 (CH_3), 28.6 (CH_3), 34.5 (HC–I), 71.5 (HC–O), 75.7 (HC–O), 79.2 (HC–O), 111.3 (C), 126.0 (CH═), 134.0 (C); IR ν_{max} (KBr)/cm^{-1}: 3450 (br), 2986, 2984, 2856, 1448, 1371, 1219, 1061, 868; EIMS *m/z* (%): 295 (20, M^+-CH_3), 235 (15, $M^+-C_3H_7O_2$), 125 (87, $M^+-C_3H_6O$–I), 108 (100, $M^+-C_3H_7O_2$–I), 79 (68), 59 (29, C_3H_7O); $[\alpha]_D^{29}$ −35 (*c* 1.07, CH_2Cl_2). Anal. required for $C_{10}H_{15}O_3I$: C, 38.73; H, 4.88%. Found: C, 38.30; H, 5.15%.

4.3.11. (1*R*,2*R*,5*R*,6*S*)-6-Iodo-1,2-*O*-isopropylidene-3-methylcyclohex-3-ene-1,2,5-triol (10b). White solid, mp: 101.2–103.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 3H), 1.42 (s, 3H), 1.79 (s, 3H), 2.05 (br s, 1H), 4.08 (dd, 1H, *J* 2.2, 9.3 Hz), 4.34 (d, 1H, *J* 4.9 Hz), 4.51 (dt, 1H, *J* 1.9, 7.4 Hz), 4.66 (dd, 1H, *J* 2.1, 5.1 Hz), 5.70 (d, 1H, *J* 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.6 (CH_3), 27.0 (CH_3), 27.8 (CH_3), 35.3 (HC–I), 70.3 (HC–O), 75.8 (HC–O), 79.2 (HC–O), 109.5 (C), 126.1 (CH═), 135.6 (C); IR ν_{max} (KBr)/cm^{-1}: 3400 (br), 2986, 1383, 1246, 1215, 1136, 1099, 1034, 871; EIMS *m/z* (%): 295 (23, M^+-CH_3), 235 (10, $M^+-C_3H_7O_2$), 211 (9), 165 (5), 127 (I^+)125 (100, $M^+-C_3H_6O$–I), 108 (62, $M^+-C_3H_7O_2$–I), 97 (27), 79 (45), 59 (33, C_3H_7O); $[\alpha]_D^{29}$ −81 (*c* 0.70, CH_2Cl_2). Anal. required for $C_{10}H_{15}O_3I$: C, 38.73; H, 4.88%. Found: C, 39.10; H, 5.26%.

4.3.12. (1*R*,2*R*,5*S*,6*R*)-6-Bromo-1,2-*O*-isopropylidene-3-methylcyclohex-3-ene-1,2,5-triol (11a). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 3H), 1.51 (s, 3H), 1.88 (s, 3H), 2.56 (d, 1H, *J* 6.2 Hz), 4.06 (m, 1H), 4.26 (m, 1H), 4.47 (m, 2H), 5.68 (d, 1H, *J* 1.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.2 (CH_3), 26.5 (CH_3), 28.5 (CH_3), 56.3 (HC–Br), 70.7 (HC–O), 76.0 (HC–O), 78.1 (HC–O), 111.2 (C), 126.5 (CH═), 133.8 (C); IR ν_{max} (KBr)/cm^{-1}: 3400 (br), 3057, 2986, 2918, 2849, 1373, 1217, 1063, 739; EIMS *m/z* (%): 247–249 (95, M^+-CH_3), 187–189 (10, $M^+-C_3H_7O_2$), 159–161 (29), 125 (35, $M^+-C_3H_6O$–Br), 108 (100, $M^+-C_3H_7O_2$–Br), 79 (52), 59 (17, C_3H_7O); $[\alpha]_D^{18}$ −46 (*c* 3.09, CH_2Cl_2). Anal. required for $C_{10}H_{15}O_3Br$: C, 45.62; H, 5.70%. Found: C, 45.77; H, 5.85%.

4.3.13. (1*R*,2*R*,5*R*,6*S*)-6-Bromine-1,2-*O*-isopropylidene-3-methylcyclohex-3-ene-1,2,5-triol (11b). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.43 (s, 3H), 1.81 (s, 3H), 2.18 (br s, 1H), 4.00 (dd, 1H, *J* 2.3, 9.0 Hz), 4.42 (d, 1H, *J* 5.1 Hz), 4.56 (ddd, 1H, *J* 1.4, 1.9, 9.0 Hz), 4.63 (dd, 1H, *J* 2.3, 5.1 Hz), 5.58 (d, 1H, *J* 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5 (CH_3), 26.8 (CH_3), 27.7 (CH_3), 55.9 (HC–Br), 69.5 (HC–O), 77.2 (HC–O), 77.8 (HC–O), 110.2 (C), 126.5 (CH═), 135.6 (C═); IR ν_{max} (KBr)/cm^{-1}: 3400 (br), 2986, 2916, 2849, 1367, 1219, 1037, 764; EIMS *m/z* (%): 247–249 (87, M^+-CH_3), 187–189 (57, $M^+-C_3H_7O_2$), 159–161 (27), 125 (29, $M^+-C_3H_6O$–Br), 108 (100, $M^+-C_3H_7O_2$–Br), 79 (54), 59 (16, C_3H_7O); $[\alpha]_D^{18}$ −99 (*c* 0.13, CH_2Cl_2). Anal. required for $C_{10}H_{15}O_3Br$: C, 45.62; H, 5.70%. Found: C, 45.23; H, 5.53%.

4.3.14. (1*R*,2*R*,3*S*,6*S*)-6-Bromine-1,2-*O*-isopropylidene-3-methylcyclohex-4-ene-1,2,3-triol (12). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 3H), 1.38 (s, 3H), 1.42 (s, 3H), 2.34 (br s, 1H), 4.39 (dd, 1H, *J* 1.0, 6.0 Hz), 4.56 (dd, 1H, *J* 2.0, 5.4 Hz), 4.88 (ddd, 1H, *J* 1.1, 2.2, 6.7 Hz), 5.95 (d, 1H, *J* 1.0, 9.8 Hz), 6.10 (ddd, 1H, *J* 0.8, 5.4, 9.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.0 (CH_3), 26.0 (CH_3), 27.1 (CH_3), 44.9 (C–Br), 68.5 (C–O), 79.8 (HC–O), 81.6 (HC–O), 109.2 (C), 129.0 (HC═), 137.4 (HC═); IR ν_{max} (KBr)/cm^{-1}: 3450 (br), 2988, 2916, 2849, 1375, 1217, 1063, 775; EIMS *m/z* (%): 247–249 (68, M^+-CH_3), 205–207 (3, $M^+-CH_3-C_3H_6$), 187–189 (30, $M^+-CH_3-C_3H_6-H_2O$), 159–161 (17), 125 (100, $M^+-CH_3-C_3H_6$–Br), 108 (67, $M^+-CH_3-C_3H_6-H_2O$–Br), 79 (27), 59 (20, C_3H_7O); $[\alpha]_D^{18}$ −239 (*c* 0.76, CH_2Cl_2).

4.3.15. (1*R*,2*R*,5*S*,6*S*)-3-Ethyl-6-iodo-1,2-*O*-isopropylidenecyclohex-3-ene-5-yl acetate (13a). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (t, 3H), 1.43 (s, 3H), 1.51 (s, 3H), 2.16 (s, 3H), 2.17 (m, 1H), 2.25 (m, 1H), 4.03 (t, 1H, *J* 9.7 Hz), 4.44 (d, 1H, *J* 5.8 Hz), 4.48 (dd, 1H, *J* 5.8, 9.8 Hz), 5.47 (dd, 1H, *J* 1.6, 3.3 Hz), 5.51 (dd, 1H, *J* 3.3, 9.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8 (CH_3), 21.4 (CH_3), 26.4 (CH_3), 26.9 (CH_2), 28.6 (CH_3), 32.0 (HC–I), 73.8 (HC–O), 74.5 (HC–O), 79.5 (HC–O), 110.8 (C), 124.0 (HC═), 140.0 (C═), 170.5 (C═O); IR ν_{max} (KBr)/cm^{-1}: 2986, 2936, 2878, 1745, 1371, 1219, 1232; EIMS *m/z* (%): 351 (27, M^+-CH_3), 249 (34, $M^+-C_3H_6O$–CH_3–C_2H_6), 239 (30, M^+-I), 197 (10, M^+-Ac–I), 181 (21.5), 139 (100), 122 (74, $M^+-C_3H_6O$–CH_3–C_2H_6–I), 111 (27), 93 (26); $[\alpha]_D^{19}$ −9 (*c* 2.44, CH_2Cl_2). Anal. required for $C_{13}H_{19}O_4I$: C, 42.62; H, 5.19%. Found: C, 42.58; H, 5.26%.

4.3.16. (1*S*,2*S*,3*R*,4*R*)-3-Ethyl-3-iodo-1,2-*O*-isopropylidenecyclohex-5-ene-4-yl acetate (14). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (t, 3H, *J* 7.5 Hz), 1.38 (s, 3H), 1.39 (s, 3H), 1.69 (m, 1H), 1.79 (m, 1H), 2.16 (s, 3H), 4.29 (d, 1H, *J* 4.9 Hz), 4.65 (ddd, 1H, *J* 1.9, 3.0, 5.0 Hz), 5.40 (dd, 1H, *J* 1.9, 3.2 Hz), 5.54 (dd, 1H, *J* 3.3, 10.3 Hz), 5.82 (dd, 1H, *J* 3.2, 10.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 6.8 (CH_3), 21.4 (CH_3), 26.9 (CH_2), 28.2 (CH_3), 30.0 (CH_3), 72.7 (HC–O), 72.9 (HC–O), 74.8 (C), 75.9 (C–O), 110.0 (C), 125.9 (HC═), 129.2 (C═), 170.5 (C═O); IR ν_{max} (KBr)/cm^{-1}: 2984, 2936, 1738, 1371, 1238, 1055, 1028; EIMS *m/z* (%): 241(21, $M^{+2}-I$), 181 (3, $M^{+2}-I-$AcOH), 169 (15, $M^{+2}-I-C_3H_6-C_2H_6$), 139 (100), 129 (57), 109 (30), 99 (34); $[\alpha]_D^{19}$ 96 (*c* 0.16, CH_2Cl_2).

4.3.17. (1*R*,2*R*,5*S*,6*R*)-6-Bromo-3-ethyl-1,2-*O*-isopropylidenecyclohex-3-ene-1,2,5-triol (15a). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (t, 3H, *J* 7.4 Hz), 1.43 (s, 3H), 1.50 (s, 3H), 2.17 (m, 1H), 2.28 (m, 1H), 4.05 (dd, 1H, *J* 7.6, 7.6 Hz), 4.30 (m, 1H), 4.44 (m, 1H), 4.56 (d, 1H, *J* 3.72 Hz), 5.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.9 (CH_3), 26.4 (CH_2), 26.4 (CH_3), 28.5 (CH_3), 57.1 (HC–Br), 71.0 (HC–O), 75.0 (HC–O), 78.2 (HC–O), 111.1 (C), 124.7 (CH═), 139.0 (C); IR ν_{max} (KBr)/cm^{-1}: 3400 (br), 3030, 2988, 1454, 1372, 1217, 1136, 1099, 1035, 871, 746, 698; EIMS *m*/*z* (%): 261–263 (28, M^+-CH_3), 201–203 (28, $M^+-C_3H_6O_2$), 173–175 (13, $M^+-C_3H_6O_2-C_2H_5$), 122 (63, $M^+-C_3H_6O$–Br), 93 (100, $M^+-C_3H_7O_2-C_2H_5$–Br); $[\alpha]_D^{29}$ −73 (*c* 0.73, CH_2Cl_2). Anal. required for $C_{11}H_{17}O_3Br$: C, 47.65; H, 6.13%. Found: C, 47.40; H, 5.90%.

4.3.18. (1*R*,2*R*,5*R*,6*S*)-6-Bromo-3-ethyl-1,2-*O*-isopropylidenecyclohex-3-ene-1,2,5-triol (15b). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (t, 3H, *J* 7.4 Hz), 1.51 (s, 3H), 1.52 (s, 3H), 2.22 (m, 2H), 3.98 (dd, 1H, *J* 9.1, 2.3 Hz), 4.50 (m, 1H), 4.56 (m, 1H), 4.64 (dd, 1H, *J* 2.9, 3.3 Hz), 5.57 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.0 (CH_3), 25.5 (CH_3), 25.7 (CH_3) 27.8 (CH_2) 56.0 (HC–Br), 69.5 (HC–O), 70.8 (HC–O), 78.3 (HC–O), 111.1 (C), 124.2 (CH═), 140.8 (C); IR ν_{max} (KBr)/cm^{-1}: 3400, 2916, 2849, 1412, 1232, 1043, 758; EIMS *m*/*z* (%): 261–263 (13, M^+-CH_3), 201–203 (21, $M^+-C_3H_6O_2$), 173–175 (13, $M^+-C_3H_6O_2-C_2H_5$), 139 (100), 122 (50, $M^+-C_3H_6O$–Br), 93 (43, $M^+-C_3H_7O_2-C_2H_5$–Br); $[\alpha]_D^{19}$ −11 (*c* 0.13, CH_2Cl_2). Anal. required for $C_{11}H_{17}O_3Br$: C, 47.65; H, 6.13%. Found: C, 47.35; H, 5.97%.

4.3.19. (1*R*,2*R*,3*S*,6*S*)-6-Bromo-3-ethyl-1,2-*O*-isopropylidenecyclohex-4-ene-1,2,3-triol (16). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (t, 3H, *J* 7.4 Hz), 1.51 (s, 3H), 1.52 (s, 3H), 2.22 (m, 2H), 3.98 (dd, 1H, *J* 9.1, 2.3 Hz), 4.50 (m, 1H), 4.56 (m, 1H), 4.64 (dd, 1H, *J* 2.9, 3.3 Hz), 5.57 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.0 (CH_3), 25.5 (CH_3), 25.7 (CH_3), 27.8 (CH_2), 56.0 (HC–Br), 69.5 (HC–O), 70.8 (HC–O), 78.3 (HC–O), 111.1 (C), 124.2 (CH═), 140.8 (C); IR ν_{max} (KBr)/cm^{-1}: 3400, 2916, 2849, 1412, 1232, 1043, 758; EIMS *m*/*z* (%): 261–263 (13, M^+-CH_3), 201–203 (21, $M^+-C_3H_6O_2$), 173–175 (13, $M^+-C_3H_6O_2-C_2H_5$), 139 (100), 122 (50, $M^+-C_3H_6O$–Br), 93 (43, $M^+-C_3H_7O_2-C_2H_5$–Br); $[\alpha]_D^{19}$ −11 (*c* 0.13, CH_2Cl_2). Anal. required for $C_{11}H_{17}O_3Br$: C, 47.65; H, 6.13%. Found: C, 47.35; H, 5.97%.

4.3.20. (1*R*,2*S*,5*S*,6*R*)-6-Bromo-3-chloro-5-hydroxycyclohex-3-ene-1,2-diyl diacetate (22a). White crystalline solid; mp 143.0–144.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.09 (s, 3H), 2.17 (s, 3H), 2.61 (d, 1H, *J* 4.9 Hz), 4.61 (dd, 1H, *J* 8.2, 11.7 Hz), 4.52 (m, 1H), 5.24 (dd, 1H, *J* 4.1, 11.7 Hz), 5.74 (d, 1H, *J* 4.1 Hz), 6.16 (d, 1H, *J* 2.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8 (CH_3), 20.9 (CH_3), 52.7 (HC–Br), 69.6 (HC–OH), 69.9 (HC–O), 73.1 (HC–O), 130.1 (C), 131.7 (CH), 169.6 (C═O), 170.1 (C═O); IR ν_{max} (KBr)/cm^{-1}: 3524, 1759, 1728, 1655, 1254, 1192, 860; EIMS *m*/*z* (%): 311 (10, M^+-CH_3), 269 (9), 251 (20, $M^+-OAc-H_2O$), 209 (57, $M^+-2(OAc)$), 187 (47), 145 (66), 43 (100); $[\alpha]_D^{28}$ −191 (*c* 0.05, CH_2Cl_2). Anal. required for $C_{10}H_{12}O_5ClBr$: C, 36.70; H, 3.66%. Found: C, 37.01; H, 4.00%.

4.3.21. (1*R*,2*S*,5*R*,6*S*)-6-Bromo-3-chloro-5-hydroxycyclohex-3-ene-1,2-diyl diacetate (22b). White solid; mp 143–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.07 (s, 3H), 2.16 (s, 3H), 3.09 (s, 1H), 4.14 (d, 1H, *J* 8.7 Hz), 4.63 (d, 1H, *J* 8.3 Hz), 5.73 (s, 2H), 6.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7 (CH_3), 20.8 (CH_3), 52.8 (HC–Br), 68.9 (HC–O), 71.0 (HC–OH), 71.9 (HC–O), 129.8 (CH), 130.5 (C), 169.8 (C═O), 170.2 (C═O); IR ν_{max} (KBr)/cm^{-1}: 3440 (br), 1751, 1649, 1236, 1219, 1144; EIMS *m*/*z* (%): 187 (35, $M^+-HBr-OAc$), 145 (100, $M^+-HBr-OAc-COCH_3$), 109 (46), 81 (18), 65 (23).

4.3.22. (1*R*,2*S*,5*S*,6*R*)-6-Bromo-3-chloro-1,2-*O*-isopropylidenecyclohex-3-ene-1,2,5-triol (23a).[16b] White crystalline solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.10 (d, 1H, *J* 4.4 Hz), 4.61 (m, 2H), 4.35 (m, 1H), 4.27 (m, 1H), 2.88 (d, 1H, *J* 9.1 Hz), 1.51 (s, 3H), 1.41 (s, 3H).

4.3.23. (1*R*,2*S*,5*R*,6*S*)-6-Bromo-3-chloro-1,2-*O*-isopropylidenecyclohex-3-ene-1,2,5-triol (23b).[19] White crystalline solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.00 (d, 1H, *J* 1.8 Hz), 4.70 (dd, 1H, *J* 9.0, 2.2 Hz), 4.60 (br d, 1H, *J* 9.7 Hz), 4.57 (dd, 1H *J* 5.1, 2.1 Hz), 4.00 (dd, 1H, *J* 9.0, 2.21 Hz), 2.42 (br s, 1H), 1.42 (s, 3H).

4.3.24. (1*R*,2*R*,5*S*,6*R*)-6-Chloro-1,2-*O*-isopropylidene-3-methylcyclohex-3-ene-1,2,5-triol (24a). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 3H), 1.52 (s, 3H), 1.89 (s, 3H), 3.96 (dd, 1H, *J* 7.6, 7.7 Hz), 4.19 (d, 1H, *J* 6.9 Hz), 4.33 (dd, 1H, *J* 6.0, 8.0 Hz), 4.47 (d, 1H, *J* 5.9 Hz), 5.66 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.2 (CH_3), 26.4 (CH_3), 28.4 (CH_3), 63.9 (HC–Cl), 70.7 (HC–O), 75.9 (HC–O), 77.9 (HC–O), 111.1 (C), 126.5 (HC═), 133.7 (C═); IR ν_{max} (KBr)/cm^{-1}: 3450 (br), 2916, 2849, 1657, 1219, 1064; EIMS *m*/*z* (%): 203–205 (83, M^+-CH_3), 143–145 (100, $M^+-C_3H_7O_2$), 125 (21, $M^+-CH_3-C_3H_6$–Cl), 115–117 (40), 107 (23, $M^+-C_3H_7O_2$–Cl), 79 (46), 59 (14, C_3H_7O); $[\alpha]_D^{18}$ −63 (*c* 0.29, CH_2Cl_2). Anal. required for $C_{10}H_{15}O_3Cl$: C, 54.94; H, 6.86%. Found: C, 54.67; H, 6.88%.

4.3.25. (1*R*,2*R*,3*S*,6*S*)-6-Chloro-1,2-*O*-isopropylidene-3-methylcyclohex-4-ene-1,2,3-triol (25). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.39 (s, 3H), 1.40 (s, 3H), 2.25 (br s, 1H), 4.36 (d, 1H, *J* 6.9 Hz), 4.46 (dd, 1H, *J* 1.8, 2.8 Hz), 4.66 (dd, 1H, *J* 2.8, 6.9 Hz), 5.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9 (CH_3), 25.4 (CH_3), 27.0 (CH_3), 54.7 (HC–Cl), 69.1 (C–O), 79.5 (HC–O), 81.6 (HC–O), 109.2 (C), 128.3 (HC═), 137.9 (HC═); IR ν_{max} (KBr)/cm^{-1}: 3450 (br), 2988, 2916, 2849, 1375, 1215, 1065, 864; EIMS (IE, 70 eV) *m*/*z* (%): 203–205 (27, M^+-CH_3), 143–145 (47, $M^+-C_3H_7O_2$), 131–133 (100), 125 (72, $M^+-CH_3-C_3H_6$–Cl), 107 (20, $M^+-C_3H_7O_2$–Cl), 95 (100), 59 (46, C_3H_7O); $[\alpha]_D^{18}$ −97 (*c* 0.44, CH_2Cl_2).

4.3.26. (1*R*,2*S*,3*R*,4*S*,5*R*,6*R*)-4-Hydroxy-3,6-diiodo-1,2-*O*-isopropylidene-3-methylcyclohex-5-yl acetate (26). Viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 3H), 1.40 (s, 6H), 2.20 (s, 3H), 4.01 (d, 1H *J* 6.7 Hz), 4.17 (d, 1H, *J* 7.2 Hz), 4.63 (dd, 1H, *J* 7.2, 3.8 Hz), 4.88 (dd, 1H, *J* 11.1, 3.3 Hz), 5.37 (dd, 1H, *J* 11.1, 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.2 (CH_3), 26.5 (CH_3), 26.7 (CH_3), 27.2 (C–I), 30.8 (C), 31.3 (CH_3), 70.3 (HC–O), 73.2 (HC–O), 77.9 (HC–O), 79.5 (HC–O), 109.2 (C), 171.0 (C═O).

4.3.27. Minor product: (1*R*,2*S*,3*S*,4*S*,5*R*,6*S*)-5-hydroxy-3,6-diiodo-1,2-*O*-isopropylidene-3-methylcyclohex-4-yl acetate (26′). Viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 3H), 1.55 (s, 6H), 2.19 (s, 3H), 4.06 (d, 1H *J* 7.2 Hz), 4.51(dd, 1H, *J* 8.6, 7.0 Hz), 4.66 (dd, 1H, *J* 7.2, 2.8 Hz), 4.81 (dd, 1H, *J* 8.6, 2.8 Hz), 5.05 (d, 1H, *J* 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.0 (C), 21.0 (CH_3), 23.5 (CH_3), 24.3 (CH_3), 25.0 (CH_3), 31.8 (C–I), 72.2 (C–O), 72.8 (C–O), 77.0 (C–O), 79.7 (C–O), 109.2 (C), 170.6 (C═O).

4.3.28. (1*R*,2*R*,3*R*,4*S*,5*S*,6*R*)-4,6-Dibromo-1,2-*O*-isopropylidene-3-methylcyclohexane-1,2,3,5-tetraol (27). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 3H), 1.57 (s, 3H), 1.74 (s, 3H), 3.96 (dd, 1H, *J* 1.6, 5.1 Hz), 4.12 (dd, 1H, *J* 3.2, 11.1 Hz), 4.26 (dd, 1H, *J* 1.7, 3.6 Hz), 4.29 (dd, 1H, *J* 8.8, 11.2 Hz), 4.52 (dd, 1H, *J* 5.1, 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.3 (CH_3), 27.9 (CH_3), 28.4 (CH_3), 59.7 (C–Br), 60.1 (C–Br), 68.9 (HC–O), 73.2 (C–O), 81.6 (HC–O), 83.4 (HC–O), 110.6 (C).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.02.109.

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