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Substituent effects in hydroxyiodination of 1,2-diacyloxycyclohex-3-enes

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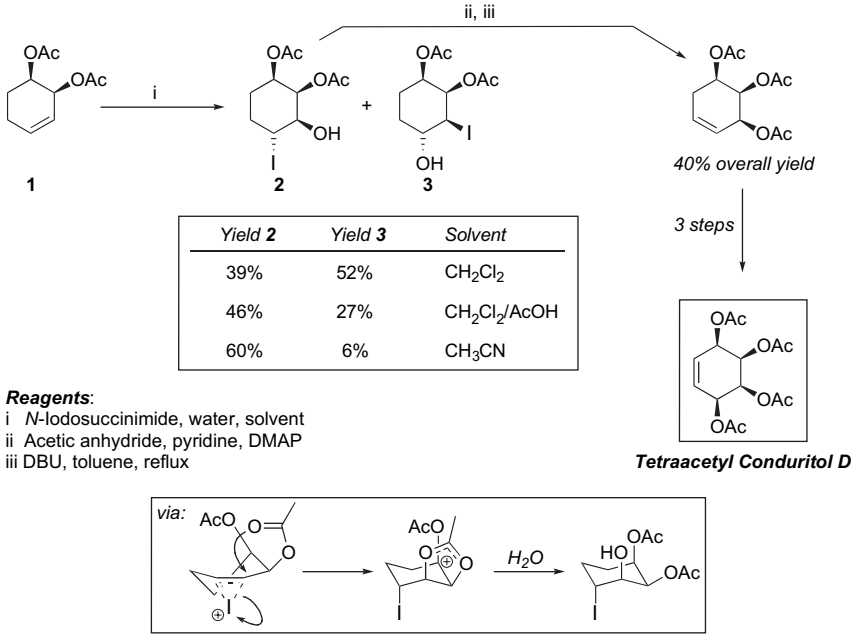
Abstract—The reaction of 1,2-diacyloxycyclohex-3-enes with iodinating agents in the presence of water has been investigated. The process is inherently diastereoselective, with many reactions giving only two of the four possible diastereoisomers which could be obtained. However, the regiocontrol is variable: highest selectivities are observed when pivalates are present on the periphery of the cycloalkene, when single regio- and diastereoisomers are obtained from the reactions.

1. Introduction

We have previously described[1] the use of iterative 1,2-hydroxyiodination reactions of acetoxycyclohexenes to prepare a conduritol D derivative;[2] during the course of that work we experienced difficulty in obtaining the desired regioselectivity in one of the crucial steps of the synthetic route to this cyclitol. Thus, the reaction of 1,2-diacetoxycyclohex-3-ene **1** with NIS in CH_2Cl_2/H_2O solvent initially gave key intermediate **2** as the minor component isolated, with diastereoisomer **3** being the primary product (Scheme 1). In other words, the diastereoselectivity of the reaction was reasonable (only two of the four possible stereoisomers were obtained) but the regioselectivity was poor and of the wrong type for our strategy. When wet acetic acid was used as cosolvent (following the precedent of



Yield **2**	Yield **3**	Solvent
39%	52%	CH_2Cl_2
46%	27%	CH_2Cl_2/AcOH
60%	6%	CH_3CN

Scheme 1.

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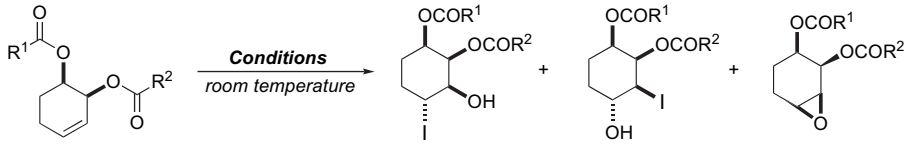
Table 1

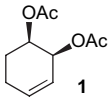
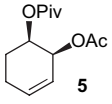
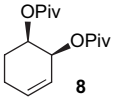


1 $R^1=R^2=Me$
5 $R^1={}^tBu$, $R^2=Me$
8 $R^1=R^2={}^tBu$

2 $R^1=R^2=Me$
6 $R^1={}^tBu$, $R^2=Me$
9 $R^1=R^2={}^tBu$

3 $R^1=R^2=Me$
7 $R^1={}^tBu$, $R^2=Me$
10 $R^1=R^2={}^tBu$

4 $R^1=R^2=Me$
11 $R^1=R^2={}^tBu$

Entry	Substrate	Conditions	Time/h	**Product** yield (%)			
1[a]	 **1**	NIS, H_2O, CH_2Cl_2	240	—	**2** 39	**3** 52	—
2[a]	**1**	NIS, H_2O, MeCN	72	—	**2** 60	**3** 6	—
3	**1**	NIS, 4 Å sieves, MeCN	144	**1** 80	**2** 1	**3** 2	—
4[a]	**1**	NIS, AcOH, CH_2Cl_2[3]	48	—	**2** 46	**3** 27	—
5	**1**	NIS, AcOH, 4 Å sieves, CH_2Cl_2	96	**1** 30	**2** 20	**3** 15	—
6	**1**	NIS, $Pb(OAc)_3\cdot H_2O$, AcOH[5]	5	—	**2** 30[b]	**3** 30[b]	—
7	**1**	I_2, AgOAc; H_2O, AcOH[6]	21	**1** 79	—	—	**4** 21
8	**2**	I_2, AgOAc; H_2O, MeCN	168	**1** 41	—	—	**4** 4
9	 **5**	NIS, H_2O, CH_2Cl_2	96	**5** 20	**6** 68	—	—
10	**5**	NIS, H_2O, MeCN	96	**5** 17	**6** 58	—	—
11	 **8**	NIS, H_2O, CH_2Cl_2	102	**8** 30	**9** 68	—	—
12	**8**	NIS, H_2O, MeCN	144	**8** 3	**9** 29	—	—
13	**8**	I_2, H_2O, CH_2Cl_2[7]	96	**8** 58	**9** 29	—	—
14	**8**	I_2, AgOAc; H_2O, AcOH	20	—	**9** 17[c]	—	**11** 25
15	**8**	I_2, AgOAc; H_2O, MeCN	24	—	**9** 26[d]	—	—

[a] Ref. 2.
[b] Inter alia.
[c] 3-Iodo-4-acetoxy analogue also obtained (55% yield).
[d] 3-Iodo-4-acetoxy analogue also obtained (27% yield).

Danishefsky et al.[3]) in the same reaction, an improvement in regiochemistry was observed, along with an inversion of selectivity: compound **2** was now obtained as the *major* isomer. Our best result was obtained when the reaction was performed using wet acetonitrile as solvent, in which case the regiocontrol was good (**2**:**3**=10:1) and the diastereocontrol maintained.

Since **2** was separable chromatographically from its diastereoisomer, the presence of by-product **3** did not seriously hinder our progression along the synthetic path leading to conduritol D, but we were of course motivated to explore the factors responsible for the variation in regioselectivity we had observed. Having briefly examined solvent effects, we next sought to investigate the effect of both alternative iodonium sources and the acyl substituent. We here describe in full[4] the results of these investigations.

2. Results and discussion

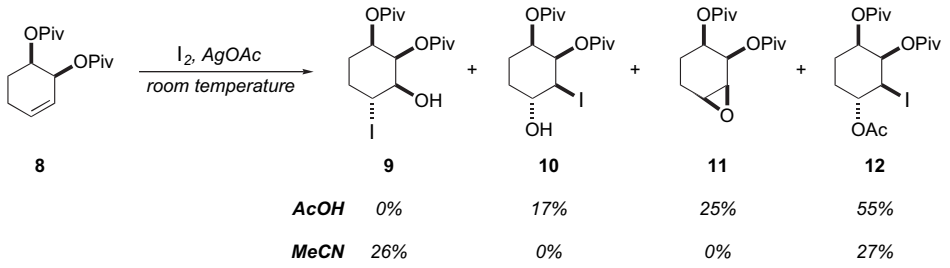
2.1. The effect of other sources of iodonium ion

We started our optimization study (Table 1) by varying the reagents employed in the reaction, but quickly found that any alteration in the source of iodonium had a deleterious effect on the process. Thus, reaction with a range of iodinating reagents proceeded very slowly, with starting materials being returned as the major constituent of the reactions. Reaction in the presence of lead acetate proceeded more rapidly than the original process, but there was no preference for **2** over **3** (Table 1, entry 6) and the reaction was difficult to work-up, returning significant amounts of intractable materials. Reaction under Prévost conditions (entries 7 and 8) was inefficient, with only **1** and epoxide **4**[†] being retrieved from the reaction mixture. Presumably the latter is formed via **2** by ring closure, under the influence of the silver(I) salt. Thus, the original source of iodonium was optimal.

2.2. The effect of 1,3-diaxial interactions

To study the effect of 1,3-diaxial interactions, we next varied the nature of the acyl substituents on the periphery of the alkene. Thus, mixed diester **5** (prepared from pivaloxycyclohexene by a sequence of hydroxyiodination, acetylation and elimination of hydroiodic acid) reacted under the conditions found to be optimal in hydroxyiodination of **1** to give a single product, *trans*-3,4-hydroxyiodide **6**, in 58% yield (or 70%, based on recovery of starting material). Now the reaction

[†] The structure of **4** was confirmed by chemical correlation with the minor epoxide obtained from epoxidation of **1** with mCPBA.



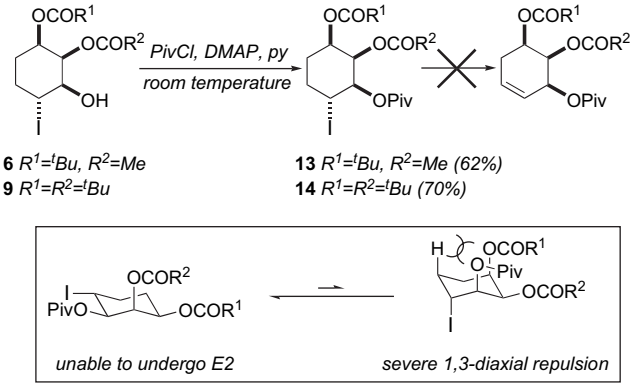
Scheme 2.

using dichloromethane as solvent was also highly selective (in contrast to the hydroxyiodination of diacetate **1**): a 68% yield (85%, based on recovered starting material) of **6** was obtained. Thus, as might be expected, it seems that increasing the steric bulk of the axial ester substituent favours formation of the α-iodonium ion, necessarily leading to **6**. What is also notable is the return of unreacted starting material from these reactions; this had been observed in similar reactions of diacetate **1** only for reactions conducted in the presence of a dessicant (entries 3 and 5) or using iodine itself as an iodinating reagent, perhaps suggesting that the crowded steric environment now retards formation of iodonium ion.

To probe this phenomenon further, we prepared dipivalate **8**, by a similar sequence to that used previously for **5**. This compound, the bulkiest diester used to date, was not completely consumed upon exposure to NIS (two portions, 2.5 equiv in total) in dichloromethane after more than 4 days at room temperature (Table 1, entry 11) and the yield of product was significantly diminished if the reaction was left past this stage. However, the reaction was highly selective, providing only the desired (from the perspective of conduritol synthesis) iodoalcohol **9** in 68% yield (entry 11, 97% yield based on recovered **8**). This process stands in stark contrast to the reaction of diacetate **1**, which proceeded with much inferior regiocontrol, although in higher yield (73–91%).

When the reaction of **8** with NIS was carried out in acetonitrile, the process was again highly selective, but not efficient: though the only product was **9**, the mass balance was poor (29% yield, 3% returned starting material). Other iodinating reagents did not efficiently produce **9**: reaction with elemental iodine gave predominantly starting material (entry 13), whilst Prévost reaction gave a mixture of products, depending upon the solvent (entries 14 and 15, Scheme 2). Thus, reaction in acetic acid proceeded in good yield (overall yield 97%) but did not give **9**, yielding instead isomer **10** and two other products, epoxide **11**[‡] (presumably formed from **9**) and (as the major product) *trans*-3,4-iodoacetate **12**. In acetonitrile solvent, **9** and **12** were formed in roughly equal amounts, implying ring opening of both α- and β-iodonium ions to be similar in energy.

Armed with a more efficient entry to the 1,2-*cis*-2,3-*cis*-3,4-*trans*-hydroxyiodides needed for conduritol synthesis, we proceeded to investigate the elimination reaction next in the synthetic sequence for conduritols. However, both mixed triester **13** and trispivalate **14** did not undergo elimination of hydroiodic acid upon treatment with a range of bases (Scheme 3). Instead, decomposition was generally observed, producing unidentifiable aromatic products. Only when the P_4-^{t}Bu base was used could products be isolated in pure form: epoxide **11** was obtained from **14** in 57% yield. Presumably in this case the *trans*-diaxial conformer required for E2 elimination is energetically inaccessible due to the crowded periphery.



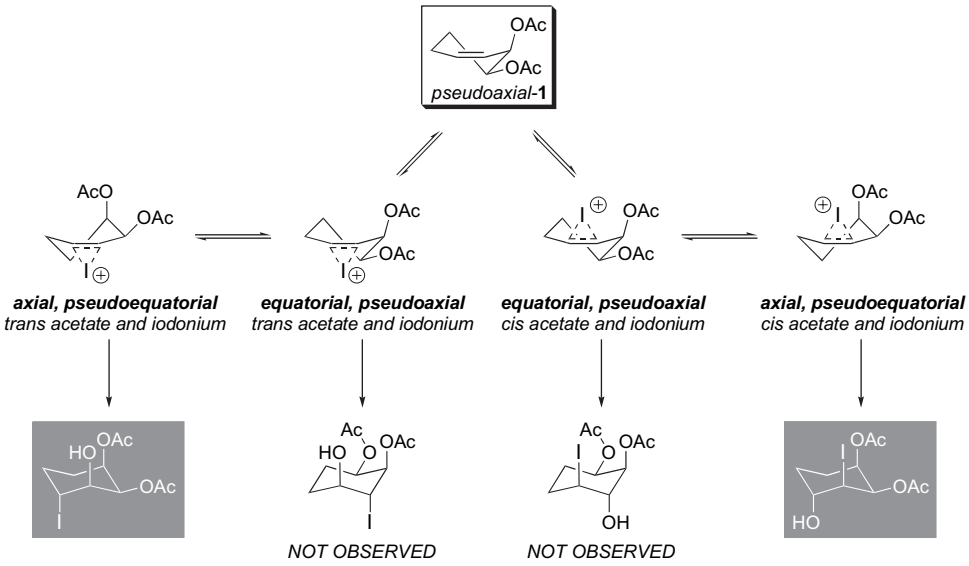
Scheme 3.

2.3. Mechanistic discussion

It is interesting to note that these reactions often proceed via apparently less stable intermediates, in Curtin–Hammett-like processes.[8] Diacetate **1** reacts through iodonium ions in which the 1-acetoxy substituent is axial, and the 2-acetoxy pseudoequatorial (Scheme 4). Thus, although one might predict that the 1-equatorial, 2-pseudoaxial conformers would be favoured, no product arising from *trans*-diaxial ring opening of such iodonium ions is obtained. It seems that the primary requirement is a pseudoequatorial allylic acyloxy group: when this condition is satisfied, formation of iodonium ion either *cis*- or *trans*-to the ring substituents is feasible and under solvent control. In a nonpolar solvent, β-iodonium is favoured, leading to 3,4-iodoalcohol product as the major product (Table 1, entry 1). When a more polar solvent, or a polar additive, is used (entries 2 and 4), α-iodonium is the favoured intermediate, leading to preferentially to *trans*-3,4-hydroxyiodides. We have previously rationalized this observation by means of nucleophilic attack of the carbonyl oxygen onto the α-iodonium, or an electrostatic stabilization of the β-iodonium ion.

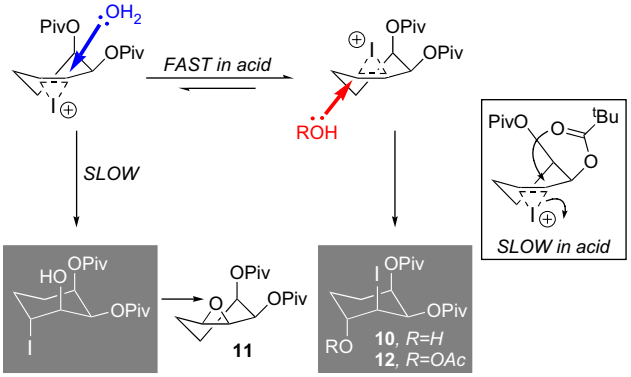
In the case of bispivalate **8**, there is a much greater preference for the α-iodonium ion, except in the Prévost reaction in acetic acid where the β-iodonium dominates. We propose

[‡] The structure of **11** was confirmed by chemical correlation with the minor epoxide obtained from epoxidation of **8** with mCPBA.



Scheme 4.

that there are two reasons for the latter observation: firstly, the equilibrium between the iodonium ions is facilitated in acid and secondly, intramolecular ring opening by the adjacent acyl group is disfavoured. Thus, the more rapid (because less hindered) diaxial ring opening to give **10** and **12** dominates, rather than the relatively slow diaxial opening of the α-iodonium by water (Scheme 5).



Scheme 5.

3. Conclusion

We have investigated the 1,2-hydoxyiodination reactions of 1,2-diacyloxycyclohex-3-enes and found them to highly selective when bulky acyl substituents are present. We are currently engaged in a detailed study of the precise mechanistic factors underlying these phenomena and we shall report in due course the results of our further studies in this arena.

4. Experimental

4.1. General techniques

All organic solvents were distilled prior to use and all reagents were purified by standard procedures.[9] 'Petrol' refers to the fraction of petroleum ether with the boiling range 40–60 °C and 'ether' refers to diethyl ether. Ether was distilled from sodium benzophenone ketyl; dichloromethane from calcium hydride. Other chemicals were purchased from Aldrich Chemical Co. or prepared by literature methods.

Melting points were recorded on either a Kofler hot-stage apparatus and are corrected, or an electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 881 spectrophotometer. Mass spectra were recorded on a Fisons Autospec spectrometer. NMR spectra were recorded on a Jeol GX-270 spectrometer, a Jeol GX-400 spectrometer or a Jeol Λ-300 spectrometer, using tetramethylsilane or chloroform as the internal standard. Chemical shifts in ^{1}H NMR spectra are expressed as parts per million downfield from tetramethylsilane, and, in ^{13}C NMR, relative to the internal solvent standard. Coupling constants (J) are quoted in Hz.

Reactions involving chemicals or intermediates sensitive to air and/or moisture were conducted under a nitrogen or argon atmosphere in flame- or oven-dried apparatus. Column chromatography was performed using Merck Kieselgel 60 or Fluka Kieselgel 60 silica gel. Analytical thin layer chromatography was carried out using either precoated Merck Kieselgel 60 F_{254} glass backed plates, or precoated Merck Kieselgel 60 F_{254} aluminium backed plates and were visualized under UV at 346 nm and/or by staining with iodine and an acidic ammonium molybdate stain (20% w/v ammonium molybdate(VI) tetrahydrate in 10% sulfuric acid).

4.1.1. (±)-*cis*-2-Acetoxy-1-(2,2-dimethylpropionyloxy)-cyclohex-3-ene (5). 1. To a solution of (±)-1,2-*cis*-2,3-*trans*-1-(2,2-dimethylpropionyloxy)-3-iodocyclohexan-2-ol[2] (1.30 g, 3.99 mmol) in pyridine (12 mL) was added acetic anhydride (0.42 mL, 4.44 mmol). The mixture was stirred at room temperature (27 h), diluted with ethyl acetate (30 mL) and washed with saturated copper(II)sulfate solution (20 mL) and water (20 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (ether/petrol, 1:4) yielded 1,2-*cis*-2,3-*trans*-2-acetoxy-1-(2,2-dimethylpropionyloxy)-3-iodocyclohexane as a colourless solid (0.96 g, 65%); R_f 0.40

[ether/petrol, 1:4]; mp 52–53 °C (Found: C, 42.63; H, 6.18; I, 34.37. $C_{13}H_{21}IO_4$ requires C, 42.40; H, 5.75; I, 34.46%); ν_{max} (CCl_4)/cm^{-1} 2954, 1754 (C=O), 1734 (C=O); δ_H (270 MHz, $CDCl_3$) 1.22 (9H, s), 1.51–2.03 (5H, m), 2.04 (3H, s), 2.46–2.51 (1H, m), 4.31 (1H, ddd, *J* 11.4, 10.3, 4.4), 5.01 (1H, dd, *J* 10.2, 3.0), 5.29–5.31 (1H, m); δ_C (67.5 MHz, $CDCl_3$) 177.29, 169.58, 76.14, 69.06, 39.03, 37.22, 28.46, 27.16, 26.20, 22.04, 20.77; *m/z* (CI) 309 (100.0), 241 ([M−I]$^+$, 13.3), 225 (5.2), 207 (9.2), 199 (5.5).

2. (±)-1,2-*cis*-2,3-*trans*-2-Acetoxy-1-(2,2-dimethylpropionyloxy)-3-iodocyclohexane (937 mg, 2.54 mmol) and DBU (0.76 mL, 5.08 mmol) in toluene (15 mL) were heated at reflux for 3 days, to yield **5** after column chromatography (ether/petrol, 1:4) as a colourless oil (469 mg, 77%); R_f 0.40 [ether/petrol, 1:4] (Found: C, 64.13; H, 8.80. $C_{13}H_{20}O_4$ requires C, 64.98; H, 8.39%); ν_{max} (CCl_4)/cm^{-1} 2973, 1732 (C=O); δ_H (270 MHz, $CDCl_3$) 1.19 (9H, s), 1.80–2.28 (4H, m), 2.05 (3H, s), 5.09 (1H, ddd, *J* 9.9, 3.5, 3.5), 5.48 (1H, m), 5.64 (1H, dddd, *J* 9.9, 4.2, 2.0, 2.0), 5.98 (1H, dddd, *J* 9.9, 4.0, 4.0, 1.0); δ_C (67.5 MHz, $CDCl_3$) 177.29, 169.96, 132.21, 123.26, 68.555, 66.365, 38.55, 26.775, 23.22, 23.06, 20.68; *m/z* (CI) 241 (MH$^+$, 2.2%), 181 (85.4), 153 (8.6), 131 (7.7), 103 (74.5) (Found 241.1451. $C_{13}H_{21}O_4$ (MH$^+$) requires 241.1440).

4.1.2. (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-2-Acetoxy-1-(2,2-dimethylpropionyloxy)-4-iodocyclohexan-3-ol 6 (Table 1, entries 9 and 10).

4.1.2.1. Method 1. To a solution of (±)-*cis*-2-acetoxy-1-(2,2-dimethylpropionyloxy)-cyclohex-3-ene **1** (100 mg, 0.416 mmol) in dichloromethane (5 mL) were added *N*-iodosuccinimide (122 mg, 0.542 mmol) and water (five drops). The mixture was stirred at room temperature (2 days), then further *N*-iodosuccinimide (94 mg, 0.418 mmol) was added and stirring continued (2 days). The mixture was washed with saturated sodium thiosulfate solution (4 mL) and the organic layer dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (ethyl acetate/petrol, 1:4) yielded unreacted **1** (20 mg, 20%) and (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-2-acetoxy-1-(2,2-dimethylpropionyloxy)-4-iodocyclohexan-3-ol **6** as a colourless solid (109 mg, 68%); R_f 0.36 [ethyl acetate/petrol, 1:4]; mp 106–107 °C (Found: C, 40.70; H, 5.70; I, 33.20%. $C_{13}H_{21}IO_5$ requires C, 40.64; H, 5.51; I, 33.03%); ν_{max} (CCl_4)/cm^{-1} 3583 (OH), 2973, 1756 (C=O), 1736 (C=O); δ_H (270 MHz, $CDCl_3$) 1.15 (9H, s), 1.69–2.03 (3H, m), 2.13 (3H, s), 2.42–2.52 (1H, m), 2.87 (1H, d, *J* 4.8), 3.85 (1H, ddd, *J* 9.9, 4.4, 3.1), 4.21 (1H, ddd, *J* 11.5, 10.2, 4.4), 4.90 (1H, ddd, *J* 10.6, 4.8, 2.75), 5.53 (1H, ddd, *J* 2.75, 2.75, 1.1); δ_C (67.5 MHz, $CDCl_3$) 177.23, 170.18, 74.52, 70.87, 69.98, 38.62, 32.78, 31.00, 26.87, 25.92, 20.77; *m/z* (CI) 385 (0.8%), 325 (34.5), 283 (5.7), 257 (18.4) (Found 385.0514. $C_{13}H_{22}IO_5$ requires 385.0512).

4.1.2.2. Method 2. To a solution of (±)-*cis*-2-acetoxy-1-(2,2-dimethylpropionyloxy)-cyclohex-3-ene **1** (100 mg, 0.416 mmol) in acetonitrile (5 mL) was added *N*-iodosuccinimide (122 mg, 0.542 mmol). The mixture was stirred at room temperature (22 h), then further *N*-iodosuccinimide (94 mg, 0.418 mmol) was added and stirring continued (4 days). Acetonitrile was removed in vacuo, the residue dissolved in dichloromethane (10 mL), and washed with saturated sodium thiosulfate solution (8 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (ethyl acetate/petrol, 1:4) yielded unreacted **1** (17 mg, 17%) and **6** (93 mg, 58%).

4.1.3. (±)-*cis*-1,2-Bis(2,2-dimethylpropionyloxy)-cyclohex-3-ene 8.

1. To a solution of (±)-1,2-*cis*-2,3-*trans*-1-(2,2-dimethylpropionyloxy)-3-iodocyclohexan-2-ol[2] (3.05 g, 9.35 mmol) in pyridine (35 mL) were added pivaloyl chloride (1.27 mL, 10.31 mmol) and DMAP (50 mg). The mixture was stirred at room temperature (2 days), at which time further pivaloyl chloride (1.15 mL, 9.34 mmol) was added and stirring continued (24 h). The mixture was then diluted with ethyl acetate (50 mL) and washed with saturated copper(II)sulfate solution (30 mL) and water (30 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (ether/petrol, 1:4) yielded unreacted starting material (124) (0.39 g, 13%) and 1,2-*cis*-2,3-*trans*-1,2-bis(2,2-dimethylpropionyloxy)-3-iodocyclohexane (2.83 g, 74%) as a colourless oil; R_f 0.70 [ether/petrol, 1:4] (Found: C, 46.54; H, 7.17; I, 31.21. $C_{16}H_{27}IO_4$ requires C, 46.84; H, 6.63; I, 30.93%); ν_{max} (CCl_4)/cm^{-1} 2935, 1736 (C=O); δ_H (270 MHz, $CDCl_3$) 1.214 and 1.215 (18H, 2×s), 1.40–2.48 (6H, m), 4.35 (1H, ddd, *J* 10.1, 10.1, 4.2), 5.00 (1H, dd, *J* 9.9, 2.7), 5.29–5.31 (1H, m); δ_C (67.5 MHz, $CDCl_3$) 176.88, 176.69, 75.57, 69.13, 40.08, 38.74, 36.935, 28.36, 27.12, 26.43, 26.17, 21.89; *m/z* (EI) 283 ([M−I]$^+$, 22.0%), 207 (3.7), 129 (4.7), 97 (12.6) (Found 283.1891. $C_{16}H_{27}O_4$ ([M−I]$^+$) requires 283.1909).

2. To a solution of (±)-1,2-*cis*-2,3-*trans*-1,2-bis(2,2-dimethylpropionyloxy)-3-iodocyclohexane (2.44 g, 5.95 mmol) in toluene (30 mL) was added DBU (1.78 mL, 11.90 mmol). The mixture was heated to reflux (30 h) until the reaction had gone to completion as evinced by ^1H NMR spectroscopy. The toluene was removed in vacuo, and the residue dissolved in dichloromethane (50 mL) and washed with 5% hydrochloric acid (30 mL) and saturated sodium hydrogen carbonate solution (30 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (ether/petrol, 1:4) yielded **8** as a colourless oil (1.33 g, 79%); R_f 0.70 [ether/petrol, 1:4] (Found: C, 67.59; H, 9.23. $C_{16}H_{26}O_4$ requires C, 68.05; H, 9.28%); ν_{max} (CCl_4)/cm^{-1} 2972, 1733 (C=O), 1619 (C=C); δ_H (270 MHz, $CDCl_3$) 1.19 and 1.21 (18H, 2×s), 1.75–2.31 (4H, m), 5.08 (1H, ddd, *J* 10.3, 3.4, 3.4), 5.41 (1H, m), 5.67 (1H, dddd, *J* 9.9, 4.4, 2.2, 2.2), 5.94 (1H, ddd, *J* 9.9, 3.2, 3.2); δ_C (67.5 MHz, $CDCl_3$) 177.39, 132.08, 123.54, 69.22, 66.43, 38.58, 27.03, 26.97, 23.66, 23.09; *m/z* (CI) 283 (MH$^+$, 24.5%), 181 (100.0), 149 (6.3) (Found 283.1899. $C_{16}H_{27}O_4$ (MH$^+$) requires 283.1909).

4.1.4. NIS/water addition to (±)-*cis*-1,2-bis(2,2-dimethylpropionyloxy)-cyclohex-3-ene 8 in dichloromethane (Table 1, entry 11); preparation of (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-1,2-Bis(2,2-dimethylpropionyloxy)-4-iodocyclohexan-3-ol 9.

To a solution of (±)-*cis*-1,2-bis(2,2-dimethylpropionyloxy)-cyclohex-3-ene **8** (100 mg, 0.35 mmol) in dichloromethane (5 mL) were added *N*-iodosuccinimide (120 mg, 0.53 mmol) and water (two drops). The mixture

was stirred at room temperature for 30 h, then further *N*-iodosuccinimide (79 mg, 1.00 mmol) and water (two drops) were added, and stirring continued for 3 days. The mixture was washed with saturated sodium thiosulfate solution (4 mL), and the organic layer dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (ether/petrol, 3:7 to 1:1) yielded unreacted **8** (30 mg, 30%) and (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-1,2-bis(2,2-dimethylpropionyloxy)-4-iodocyclohexan-3-ol **9** as a colourless solid (102 mg, 60%); R_f 0.38 [ether/petrol, 3:7]; mp 137–138 °C; ν_{max} (CCl_4)/cm^{-1} 3583 (OH), 2974, 1743 (C=O); δ_H (270 MHz, $CDCl_3$) 1.15 and 1.25 (18H, 2×s), 1.70–1.87 (2H, m), 1.97–2.12 (1H, m), 2.43–2.50 (1H, m), 2.51 (1H, br s), 3.85 (1H, ddd, *J* 10.1, 3.5, 2.9), 4.16 (1H, ddd, *J* 11.5, 10.3, 4.4), 4.91 (1H, ddd, *J* 10.9, 4.6, 2.4), 5.49 (1H, ddd, *J* 2.75, 2.75, 1.1); δ_C (67.5 MHz, $CDCl_3$) 177.48, 177.29, 75.03, 70.65, 70.21, 39.04, 38.65, 32.63, 31.38, 27.25, 27.16, 27.00; *m/z* (CI) 427 (MH^+, 8.5%), 325 (100.0), 299 (24.9) (Found 427.0982. $C_{16}H_{28}IO_5$ (MH^+) requires 427.0982).

4.1.5. I_2/water addition to (±)-*cis*-1,2-bis(2,2-dimethylpropionyloxy)-cyclohex-3-ene 8 in dichloromethane (Table 1, entry 13). To a solution of (±)-*cis*-1,2-bis(2,2-dimethylpropionyloxy)-cyclohex-3-ene **8** (50 mg, 0.177 mmol) in dichloromethane (2 mL) were added iodine (67 mg, 0.264 mmol) and water (five drops). The mixture was stirred at room temperature (23 h), then further iodine (50 mg, 0.197 mmol) and water (two drops) was added and stirring continued for 3 days. The mixture was washed with saturated sodium thiosulfate solution (2 mL), and the organic layer dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (ether/petrol, 3:7) yielded (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-1,2-bis(2,2-dimethylpropionyloxy)-4-iodocyclohexan-3-ol **9** (22 mg, 29%) and unreacted **8** (29 mg, 58%).

4.1.6. (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-4-Acetoxy-1,2-bis(2,2-dimethylpropionyloxy)-3-iodocyclohexane 12 (Table 1, entries 14 and 15).

4.1.6.1. Method 1. To a solution of (±)-*cis*-1,2-bis(2,2-dimethylpropionyloxy)-cyclohex-3-ene **8** (50 mg, 0.177 mmol) in acetonitrile (2 mL) were added acetic acid (0.02 mL, 0.354 mmol) and silver(I)acetate (59 mg, 0.354 mmol) followed by iodine pellets (67 mg, 0.264 mmol). The mixture was stirred at room temperature (24 h), filtered and concentrated in vacuo. The residue was dissolved in ethyl acetate (10 mL), washed with saturated sodium hydrogen carbonate solution (6 mL) and brine (6 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (20%-ether/petrol, 3:7) yielded **9** (20 mg, 26%) and (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-4-acetoxy-1,2-bis(2,2-dimethylpropionyloxy)-3-iodocyclohexane **12** as a colourless solid (22 mg, 27%); R_f 0.50 [ether/petrol, 1:4]; mp 116–117 °C (corrected) (Found: C, 45.53; H, 6.40; I, 26.90. $C_{18}H_{29}IO_6$ requires C, 46.16; H, 6.24; I, 27.10%); ν_{max} (CCl_4)/cm^{-1} 2975, 1747 (C=O), 1737 (C=O); δ_H (270 MHz, $CDCl_3$) 1.14 and 1.31 (18H, 2×s), 1.40–1.55 (1H, m), 1.85–1.99 (1H, m), 2.10 (3H, s), 2.14–2.34 (1H, m), 4.21 (1H, dd, *J* 11.0, 2.6), 4.91 (1H, ddd, *J* 11.2, 5.3, 2.75), 5.09 (1H, ddd, *J* 10.8, 10.8, 4.8), 5.65–5.67 (1H, m); δ_C (75 MHz, $CDCl_3$) 177.47, 176.29, 169.90, 72.70, 72.40, 70.05, 39.19, 38.67, 28.82, 28.49, 27.46, 27.04, 23.65, 21.11; *m/z* (EI) 341 ($[M-I]^+$, 4.5%), 306 (4.4), 281 (7.8), 197 (12.5) (Found 341.1977. $C_{18}H_{29}O_5$ ($[M-I]^+$) requires 341.1964).

4.1.6.2. Method 2. To a solution of (±)-*cis*-1,2-bis(2,2-dimethylpropionyloxy)-cyclohex-3-ene **8** (50 mg, 0.177 mmol) in acetic acid (2 mL) was added silver(I) acetate (59 mg, 0.354 mmol) and water (five drops) followed by iodine (67 mg, 0.264 mmol). The mixture was stirred at room temperature (20 h), filtered and concentrated in vacuo. The residue was dissolved in ethyl acetate (10 mL), washed with saturated sodium hydrogen carbonate solution (6 mL) and brine (6 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (ether/petrol, 1:4) yielded **12** (46 mg, 55%), (±)-1,2-*cis*-2,3-*cis*-3,4-*cis*-1,2-bis(2,2-dimethylpropionyloxy)-3,4-epoxycyclohexane **11** (13 mg, 25%) and (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-1,2-bis(2,2-dimethylpropionyloxy)-3-iodocyclohexan-4-ol **12** (13 mg, 17%).

4.1.7. (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-1,2,3-Tris(2,2-dimethylpropionyloxy)-4-iodocyclohexane 14. To a solution of (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-1,2-bis(2,2-dimethylpropionyloxy)-4-iodocyclohexan-3-ol **9** (455 mg, 1.067 mmol) in pyridine (5 mL) were added pivaloyl chloride (0.2 mL, 1.624 mmol) and DMAP (30 mg). The mixture was stirred at room temperature (24 h), then further pivaloyl chloride (0.2 mL, 1.624 mmol) was added and stirring continued for 3 days. The mixture was then diluted with ethyl acetate (30 mL) and washed with saturated copper(II)sulfate solution (20 mL) and water (20 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (ether/petrol, 1:4) yielded **14** as a colourless solid (380 mg, 70%); R_f 0.57 [ether/petrol, 1:4]; mp 176–177 °C (corrected) (Found: C, 49.87; H, 6.74; I, 24.26. $C_{21}H_{35}IO_6$ requires C, 49.42; H, 6.71; I, 24.86%); ν_{max} (CCl_4)/cm^{-1} 2976, 1745 (C=O); δ_H (270 MHz, $CDCl_3$) 1.14, 1.21 and 1.27 (27H, 3×s), 1.60–1.88 (2H, m), 2.04–2.20 (1H, m), 2.52–2.61 (1H, m), 4.20 (1H, ddd, *J* 12.6, 11.3, 4.6), 4.94 (1H, ddd, *J* 11.5, 5.5, 2.6), 5.01 (1H, dd, *J* 11.4, 2.6), 5.47 (1H, ddd, *J* 2.75, 2.75, 1.3); δ_C (67.5 MHz, $CDCl_3$) 176.89, 176.39, 176.32, 74.95, 69.62, 69.44, 38.90, 38.68, 38.54, 33.81, 27.24, 27.04, 26.90, 26.43, 23.00; *m/z* (EI) 409 (0.7%), 393 (1.1), 385 (1.5), 383 ($[M-I]^+$, 40.6), 197 (9.1) (Found 383.2430. $C_{21}H_{35}O_6$ ($[M-I]^+$) requires 383.2434).

4.1.8. (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-2-Acetoxy-1,3-bis(2,2-dimethylpropionyloxy)-4-iodocyclohexane 13. Prepared as for (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-1,2,3-tris(2,2-dimethylpropionyloxy)-4-iodocyclohexane **14**, but from (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-2-acetoxy-1-(2,2-dimethylpropionyloxy)-4-iodocyclohexan-3-ol **6** (205 mg, 0.534 mmol), pivaloyl chloride (0.07 mL initially, then an additional 0.07 mL after 19 h, 1.136 mmol total) and DMAP (20 mg) in pyridine (4 mL) with stirring at room temperature (2 days) to yield unreacted alcohol **6** (21 mg, 10%) and **15** as a colourless solid (155 mg, 62%); R_f 0.54 [ethyl acetate/petrol, 1:4]; mp 129.5–130.5 °C (corrected); ν_{max} (CCl_4)/cm^{-1} 2978, 1757 (C=O), 1744 (C=O); δ_H (270 MHz, $CDCl_3$) 1.13 and 1.20 (18H, 2×s), 1.65–1.90 (2H, m), 2.00–2.13 (1H, m), 2.12 (3H, s), 2.49–2.58 (1H, m), 4.22

(1H, ddd, *J* 12.8, 11.6, 4.6), 4.91 (1H, ddd, *J* 11.7, 5.1, 2.9), 4.97 (1H, dd, *J* 11.4, 2.8), 5.49 (1H, ddd, *J* 2.75, 2.75, 1.3); δ_C (67.5 MHz, $CDCl_3$) 176.97, 176.39, 169.40, 74.71, 69.57, 69.28, 38.71, 38.58, 33.66, 27.08, 26.97, 26.85, 26.43, 22.92; *m/z* (EI) 341 ([M−I]$^+$, 15.5%), 264 (1.4), 193 (4.2), 189 (5.1), 137 (8.7), 113 (4.6) (Found 341.1962. $C_{18}H_{29}O_6$ ([M−I]$^+$) requires 341.1964).

4.1.9. Attempted elimination of HI from (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-1,2,3-Tris(2,2-dimethylpropionyloxy)-4-iodocyclohexane 14. To a solution of (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-1,2,3-tris(2,2-dimethylpropionyloxy)-4-iodocyclohexane **14** (60 mg, 0.118 mmol) in THF (2 mL) at −78 °C was added, dropwise, a solution of phosphazene P_4-^{t}Bu base (152) (0.12 mL of a 1 M solution in hexane, 0.12 mmol) in THF (0.5 mL). The mixture was stirred at −78 °C (2 h), then to room temperature (20 h). Solvent was removed in vacuo, and ether (10 mL) was added to the residue. The resultant precipitate was filtered and washed with ether (4×10 mL). The combined filtrates were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (20%-ether/petrol, 3:7) yielded (±)-1,2-*cis*-2,3-*cis*-3,4-*cis*-1,2-bis(2,2-dimethylpropionyloxy)-3,4-epoxycyclohexane **11** (20 mg, 57%) as the only isolable product.

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