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LETTERS

Factors Influencing The Regiochemistry of Hydroxyiodination of 1,2-Diacyloxycyclohex-3-enes

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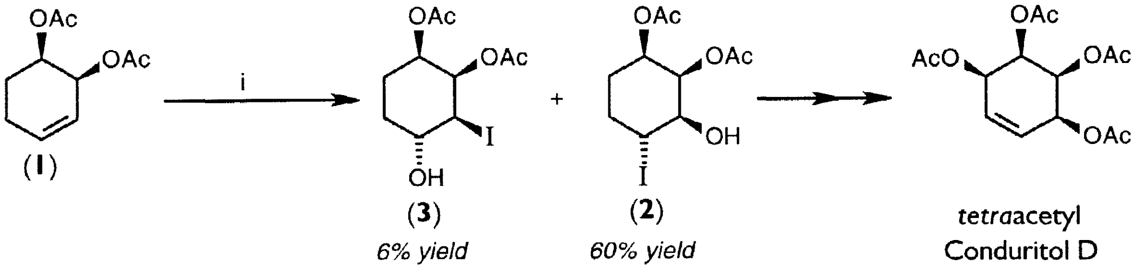
Abstract

The 3,4-hydroxyiodination of 1,2-diacyloxycyclohex-2-enes has been reinvestigated: the nature of the source of positive iodine does not appear to have a pronounced effect upon regiocontrol. Using bulkier acyl substituents, the regiocontrol of the process could be vastly improved. © 1998 Published by Elsevier Science Ltd. All rights reserved.

Keywords: Hydroxyiodination, conduritol D, conformational control

1. Introduction

We recently reported a synthesis of *tetra*acetyl Conduritol D[1] based upon iterative stereoselective 1,2-iodohydroxylation reactions of acetoxycyclohexenes.[2] In one of the key steps of this reaction sequence, 1,2-diacetoxycyclohex-3-ene (**1**) underwent such selective reaction to give 1,2-*trans*-2,3-*cis*-3,4-*cis*-3,4-diacetoxy-1-iodocyclohexan-2-ol (**2**) as the major product, but (**2**) was always contaminated with its regioisomer (**3**). Serendipitously, (**2**) is separable from (**3**) by flash chromatographic techniques, but we were, of course, motivated to optimize this reaction to enhance the selectivity still further: in this *Letter*, we report the preliminary results of our investigations towards that goal.



Conditions: i *N*-Iodosuccinimide, water, CH_3CN, room temp.

Scheme 1

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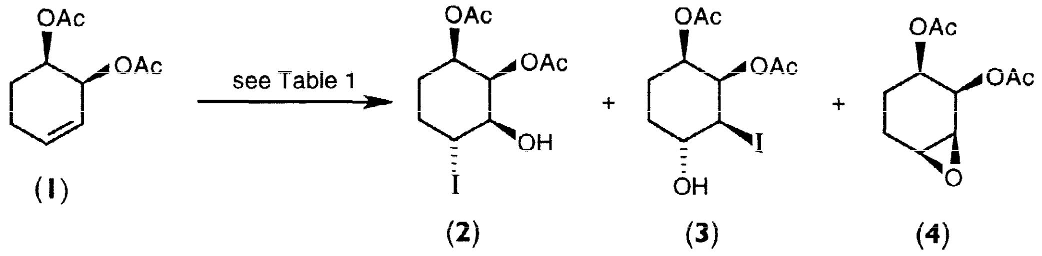
2. Results and discussion

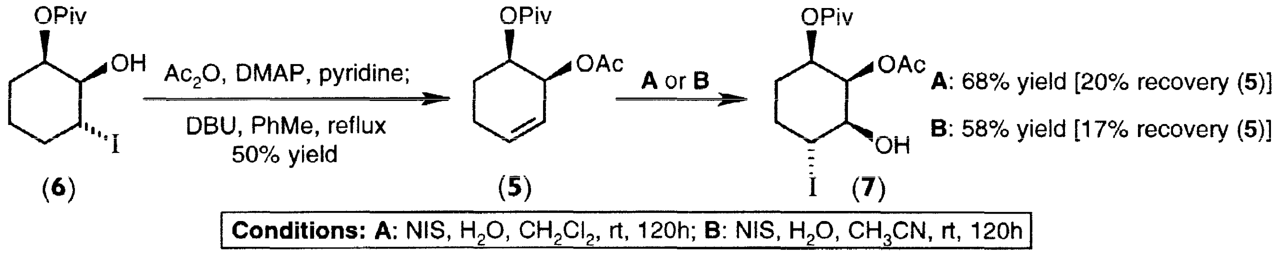


Entry	Conditions	Yield **1**/%	Yield **2**/%	Yield **3**/%	Yield **4**/%
1	A	0	39	52	0
2	B	0	60	6	0
3	C	0	46	27	0
4	D	30	30	30	0
5	E	30	20	15	0
6	F	80	1	2	0
7	G	79	0	0	21
8	H	41	0	0	4

Conditions: **A**: NIS, H_2O, CH_2Cl_2, rt, 240 h; **B**: NIS, H_2O, CH_3CN, rt, 72 h; **C**: NIS, AcOH, CH_2Cl_2, rt, 48 h; **D**: NIS, AcOH 4Å ms, CH_2Cl_2, 96 h; **E**: NIS, $Pb(OAc)_3 \cdot H_2O$, AcOH, rt, 5h; **F**: NIS, 4Å ms, CH_3CN, rt, 144 h; **G**: I_2, AgOAc, H_2O, AcOH, rt, 21h; **H**: I_2, AgOAc, H_2O, CH_3CN, rt, 168 h.

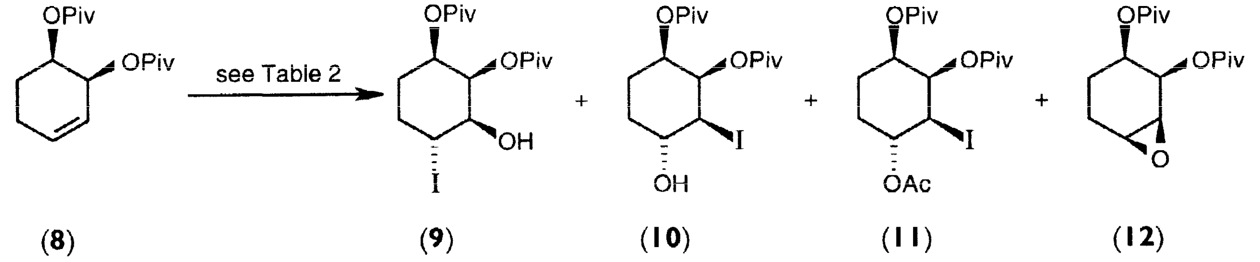
Table 1

Our observations are collated in Tables 1 and 2. Thus, for the iodohydroxylation of (**1**), a rather slow reaction requiring 72 hours for all starting materials to be consumed, acetonitrile was found to be the most appropriate solvent for preferential obtention of the desired regio- and diastereoisomer (**2**). Use of dichloromethane as solvent (Table 1, entry 1) caused both a drastic retardation in the rate of consumption of starting materials (240 hours now being required for complete reaction), and favoured the undesired regioisomer. This preference was inverted and the reaction proceeded much more quickly (starting materials being consumed in 48 hours) when a small amount of glacial acetic acid[3] was added to the CH_2Cl_2-solvated reaction (100:1 v/v CH_2Cl_2:AcOH), but the selectivity of the transformation remained poor (approximately 1.7:1 in favour of (**2**)). Under anhydrous conditions (i.e. in the presence of molecular sieves, table 1, entry 4), the same reaction proceeded significantly more slowly, and returned considerable amounts (30%) of starting material. When the most selective iodohydroxylation reaction conditions so far identified were re-employed under strictly anhydrous conditions (table 1, entry 6) only trace amounts of products arising from successful reaction were observed. When $Pb(OAc)_3$[4] was employed in the reaction, a much more rapid reaction was observed, but the starting materials were not consumed and there was no selectivity shown in iodohydroxylation. Use of Prévost-like conditions gave mainly starting material: epoxide **4** (presumably produced by cyclization of **2**) was the only other species isolated from the reaction mixture, in mediocre yield.



Scheme 2

We next investigated the effect of the steric demand of the acyl substituents present. Thus, mixed diester **5**, prepared from hydroxyiodide **6**,[1] was subjected to the iodohydroxylation reaction. We were pleased to witness a highly selective reaction of **5**, with hydroxyiodide **7** being the only product of the reaction, even using the conditions (conditions **A**) which had proved troublesome when diacetate **1** had been used. To examine the influence of a larger acyl substituent at the postulated site of neighbouring group participation, dipivalate **8** was prepared. Its reactions with a variety of reagents are summarized in table 2.



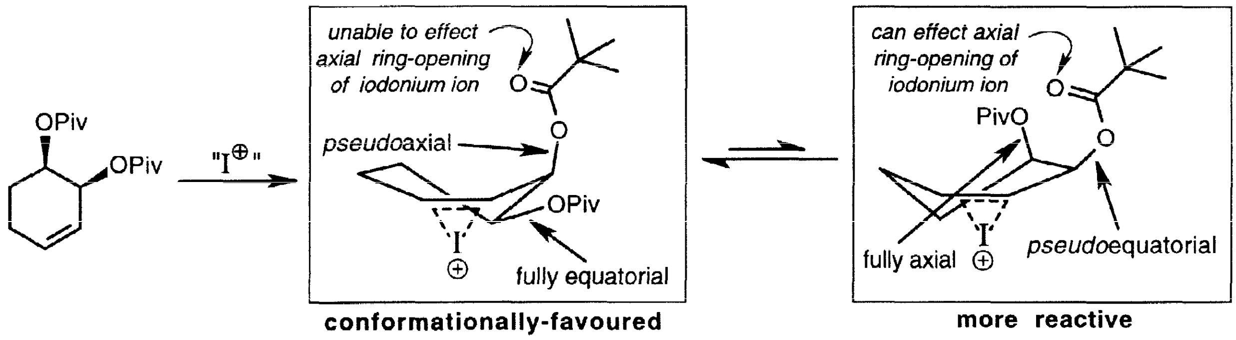
Entry	Conditions	Time/h	Yield **8**/%	Yield **9**/%	Yield **10**/%	Yield **11**/%	Yield **12**/%
1	A	72	30	68	0	0	0
2	B	144	3	29	0	0	0
3	C	96	58	29	0	0	0
4	D	24	0	26	0	27	0
5	E	20	0	0	17	55	25

Conditions: **A** NIS, H_2O, CH_2Cl_2, rt; **B** 1. NIS 2. H_2O, CH_3CN, rt; **C** I_2, H_2O, CH_2Cl_2, rt; **D** I_2, AgOAc, H_2O, CH_3CN, rt; **E** I_2, AgOAc, H_2O, AcOH, rt

Table 2

Thus, using 'normal' iodohydroxylation conditions, a good yield of the desired regioisomer **9** was obtained and the reaction was faster than before (table 2, entry 1). Using the more polar 'normal' conditions (entry 2), decomposition was the predominant process and the yield of **9** was poor. Reaction of **8** with elemental iodine under a variety of conditions gave **9** in variable yield: when no other additive was present, iodine/water gave **9** in mediocre yield, with the predominant species isolated being recovered starting material (entry 3). Prévost reaction of **8** in acetonitrile solvent gave both **9** and **11** in moderate overall yield as a 1:1 mixture (entry 4), but a similar reaction in the presence of acetic acid, rather than acetonitrile, gave none of the desired hydroxyiodide (entry 5). Under these reaction conditions, there was a virtually quantitative yield, with **11** now being the major product of the reaction, the other products being **10** (a regioisomer of **9**) and epoxide **12** (arising from cyclization of **9**).

Although more detailed investigation is required to ascertain the exact course of events, we tentatively suggest that these data might indicate that the reactions of **6** and **8** still proceed *via* an intramolecular delivery of oxygen (as first postulated[5]) under a Curtin-Hammett effect[6] (scheme 3), although, of course, the iodonium ion may not necessarily be conformed in a half-chair The precise nature of the mechanistic nuances of these reactions are currently under investigation in our lab.



Scheme 3

Acknowledgements

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