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Mechanistic Studies on the Diastereoselective Halohydroxylation of γ-δ Unsaturated Carboxamides

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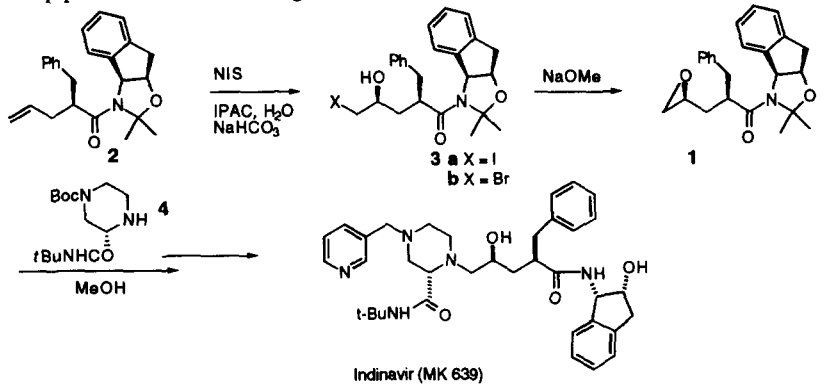
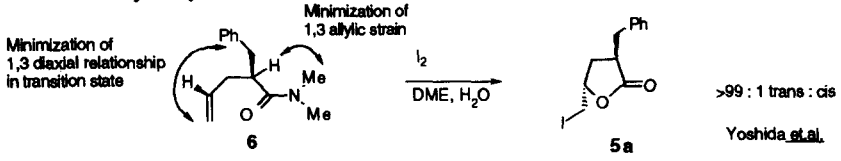
Abstract: *Evidence is presented that the diastereoselective iodohydroxylation of the the γ-δ unsaturated amide 2 proceeds without involvement of iminium ion 12 directly to the tetrahedral intermediate 17 and its subsequent endocyclic cleavage to 3.* Copyright © 1996 Elsevier Science Ltd

We recently reported that the iodohydroxylation of γ-δ unsaturated carboxamides occurs with efficient 1,3 chirality transfer producing iodohydrins in high yield.[1] The synthetic utility of this reaction is exploited in the large scale manufacture of the HIV protease inhibitor Crixivan® (Indinavir, MK 639, L-735,524)[2] to produce the epoxide intermediate **1**. The γ-δ unsaturated carboxamide **2** is transformed into the iodohydrin **3a** in a biphasic aqueous $NaHCO_3$/ EtOAc system with N-iodosuccinimide (NIS). Treatment of **3** with base leads to **1** which is coupled with the piperazine **4**[3] to set the stage for the final elaboration of Indinavir.[4]

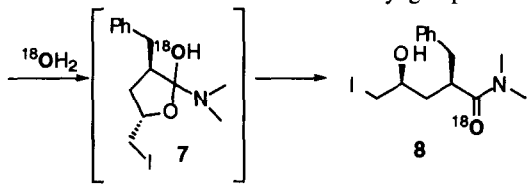


The high diastereoselectivity (97:3) of the 1,3 induction parallels the work of Yoshida,[5] who observed the formation of trans- iodomethyl butyrolactone **5a** in the reaction of **6** with unbuffered I_2 in aqueous DME. The diastereoselectivity was a result of the avoidance of 1,3-allylic and 1,3-diaxial interactions[6] in the transition state. Under Yoshida's strongly acidic reaction conditions hydrolysis produced the butyrolactone **5a**; the virtual absence of butyrolactone product using our biphasic iodohydroxylation conditions with NIS prompted further investigation of the iodohydroxylation reaction.

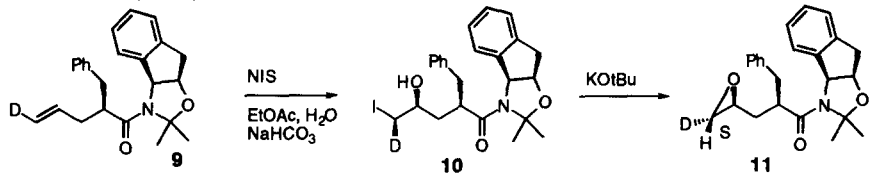


As has been reported,[1] the scope of the diastereoselective iodohydroxylation extends beyond substrate **2** and is a general reaction for 2-alkyl-4-enamides. Additionally, the reaction is not limited to NIS or NCS and NaI - other forms of positive halogen such as HOI or HOBr[7] (prepared from HgO and I_2 or Br_2) perform equally well in the diastereoselective halohydroxylation of **2** to give the corresponding iodohydrin **3a** (96% yield) and bromohydrin **3b** (86% yield).

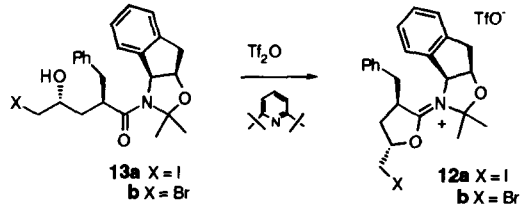
During the iodohydroxylation reaction the elements of HOI are added across the olefin. In order to check the origin of the newly formed hydroxyl, the reaction was performed with **6** in ^{18}O-labeled H_2O. Analysis of the MS fragmentation pattern of **8** showed that ^{18}O was incorported into the amide carbonyl group,[8] as would be expected from the existence of a tetrahedral intermediate **7**. This result rules out a simple addition of HOI across the double bond and requires the intimate involvement of the amide carbonyl group in the mechanism.



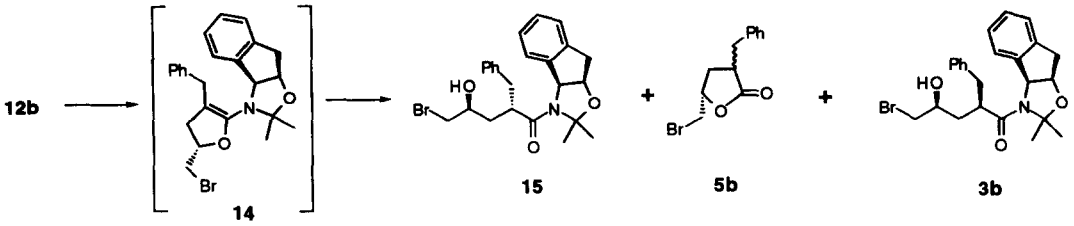
The stereochemical course of the addition of HOI to the olefin was examined by preparing the deuterium labeled compound **9**.[9] Under standard iodohydroxylation conditions **9** was first converted to the iodohydrin **10** and subsequently to a single epoxide **11**. Using NOE difference spectroscopy it was possible to assign the stereochemistry of the new chiral center as *S*.[10] Thus the conclusion is that I^+ adds to the outside (*re, re*) face of the olefin **9** in the iodohydroxylation reaction and I and OH are added to opposite faces of the olefin.



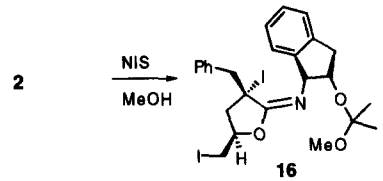
From these results it would appear that the iminium ion **12** could be an intermediate on the reaction pathway of the iodohydroxylation. To ascertain whether iminium ion **12** is indeed an intermediate, it was generated independently by treating the epi-bromohydrin **13b**[11] with Tf_2O and 2,6-di-*tert*-butylpyridine in $CDCl_3$ which cleanly resulted in the iminium ion **12b**.[12]



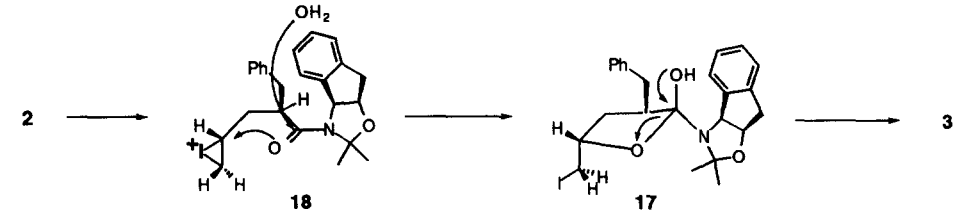
Submission of **12b** to the buffered aqueous biphasic conditions of the halohydroxylation ($EtOAc/NaHCO_3$, H_2O) produced the epi-benzyl derivative **15** (37%), the cis- and trans-butyrolactones **5b** (15 %) and finally a small amount of **3b** (7%). If the iminium ion **12** were an intermediate in the halohydroxylation, clean formation of **3b** would have been expected. Indeed, the isolated products are consistent with tautomerization of **12b** to the enamine **14** and subsequent hydrolysis.



Ancillary evidence for the absence of an iminium ion was obtained in the reaction of **2** with NIS (2 equiv.) in MeOH, which formed **16** in 75% yield.[13] A plausible reaction path to **16** is the formation of an iminium ion **12a** followed by acetonide cleavage and subsequent iodination of the enamine tautomer of the imine. If the iminium ion **12a** were involved in the iodohydroxylation, an analogous acetonide cleavage and iodination would be expected but it is not observed.



The evidence points to a mechanism for the iodohydroxylation whereby addition of I^+ to the outside face of the olefin, addition of the amide carbonyl to the iodonium ion **18**, and addition of OH^- to the amide carbonyl all occur without the involvement of an iminium ion intermediate **12**. The initial stage of the reaction is thus best represented as the direct formation of the tetrahedral intermediate **17** from the iodonium ion **18** derived from **2**.



Inspection of models of **12** show a severe $A^{1,3}$ strain. Thus, the iminium ion **12** is presumably a strained species and the avoidance of this strain build-up in the reaction path of the halohydroxylation leads to the direct formation of the tetrahedral intermediate **17**.

The collapse of tetrahedral intermediate **17** is selective for endocyclic cleavage to **3**; only traces of the lactone are formed by exocyclic cleavage and loss of the aminoindanol. The electron-withdrawing halomethyl group is expected to increase the ring oxygen's leaving group ability as compared to an unsubstituted alcohol. Additionally, endocyclic cleavage is expected on the basis of the Antiperiplanar Lone Pair Hypothesis, in that the endocyclic C-O bond is parallel to a lone pair both on the OH and on the N after a simple rotation around the C-N bond.[14]

In summary, the mechanism of the iodohydroxylation of **2** to **3** can be understood as a direct formation of the tetrahedral intermediate **17** from **2**, followed by the stereoelectronically controlled endocyclic cleavage of **17** to **3**.

References and Notes

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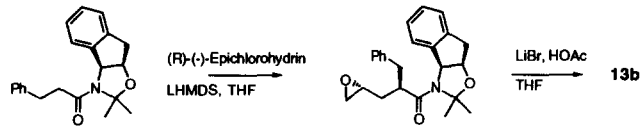
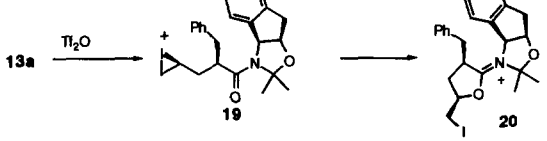
8. Water is lost for both labelled and unlabelled material as $H_2{}^{16}O$, the amide CO containing fragment is different by 2 mass units: 361 (^{16}O M^+), 363 (^{18}O M^+); 343 (^{16}O M^+ - $H_2{}^{16}O$), 345 (^{18}O M+ - $H_2{}^{16}O$); 72 ($Me_2NC^{16}O$), 74 ($Me_2NC^{18}O$).
9. The following scheme was used to prepare **9**:

10. Proton spin-spin coupling constants and NOE difference experiments were used to assign the epoxide methylene protons in protio **11**. Comparison with mono-deutero **11** permits the stereochemical assignments as shown.
11. The following scheme was used to prepare **13b**:



12. **12b**: ^{13}C NMR (C_6D_6, 100.5 MHz) δ 178.2, 141.5, 136.5, 136.3, 129.2, 129.0, 128.8, 127.2, 125.9, 125.3, 103.0, 89.8, 82.1, 70.2, 46.6, 37.0, 35.3, 31.6, 31.5, 25.7, 24.1. The regiochemistry of the imidate and the relative stereochemistry in the five-membered ring were determined using NOE difference spectroscopy.
(b) Epimerization (ca. 50%) of the iodomethyl sidechain was observed in the analogous preparation of the iodo compound **12a**. Competitive displacement of the triflate by the neighboring iodine and opening of the resulting iodonium ion **19** by the amide carbonyl led to an epimerized iodomethyl group in **20**:



13. (a) **16**: ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 161.8, 142.4, 140.4, 136.5, 130.7, 128.0, 127.7, 126.8, 126.4, 125.7, 124.5, 100.5, 76.5, 73.3, 62.2, 48.8, 47.4, 46.8, 44.7, 37.2, 25.5, 24.7, 6.9. The relative stereochemistry of the five-membered ring was determined using NOE difference spectroscopy.
(b) Kitagawa, O.; Hanano, T.; Hirata, T.; Inoue, T.; Taguchi, T. *Tetrahedron Lett.* **1992**, *33*, 1299.
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