

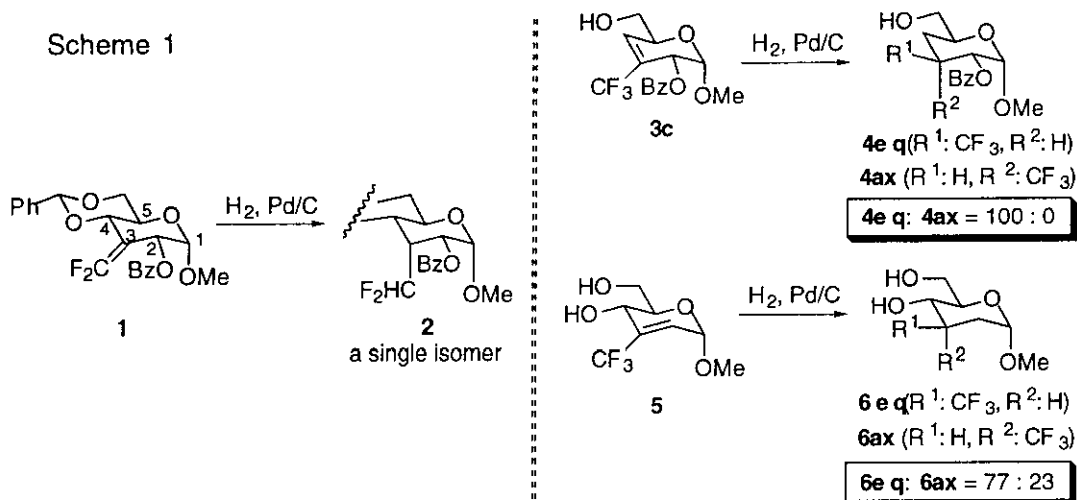
STERESELECTIVE HYDROGENATION OF D-GLUCOSE-DERIVED *ENDO*-OLEFINS WITH A CF₃ GROUP
--EXPERIMENTAL AND THEORETICAL EXPLANATIONS--[#]

Shuichi Hiraoka, Takashi Yamazaki,* and Tomoya Kitazume

Department of Bioengineering, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama 226, Japan

Abstract- The unexpected high diastereofacial selectivity in hydrogenation of *endo*-olefins bearing a CF₃ group by Pd/C under a hydrogen atmosphere was discussed on the basis of experimental results as well as semiempirical molecular orbital calculations.

We have recently developed the novel methods¹ to stereoselectively introduce various types of fluorine-containing methyl groups (CH_{3-n}F_n; n=1-3) at 3 position of D-glucose derivatives, where catalytic hydrogenation played a pivotal role for attainment of the high diastereofacial selection (Scheme 1). For example, compound (**1**) was converted to the corresponding saturated form (**2**) as a single stereoisomer almost in a quantitative yield. Considering that the methoxy group possesses the axial location by virtue of the anomeric effect,² the observed stereoselection at 3 position would be understood as a result of the preferential approach of the Pd catalyst from the more vacant *si* (upper) face. In the case of monocyclic



[#] Dedicated to Professor Koji Nakanishi on the occasion of his 75th birthday.

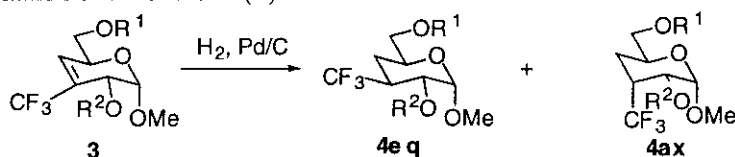
endo-olefins (**3c**) or (**5**), since all the ring substituents at sp^3 carbon atoms were considered to occupy the psuedo-equatorial position except for the psuedo-axially disposed methoxy group, we anticipated the similar stereochemical outcome by the Pd-catalyzed hydrogenation, leading to the exclusive formation of **4ax** or **6ax**, respectively. However, from the NMR analyses of the products, this was not the case and hydrogenation in fact occurred exclusively (for **3c**) or mainly (for **5**) from the more hindered opposite side to furnish the unexpected products (**4eq**) or (**6eq**). In this communication, we would like to report the rationalization of this "unusual" stereoselectivity on the basis of experimental results as well as theoretical calculations.

At first, we briefly investigated the effects of 2-*O*- and 6-*O*- protective groups of **3** on the diastereofacial selectivity, whose results are summarized in Table 1. In the case of large R^1 groups like trityl (Tr, **3a**) or *tert*-butyldimethylsilyl (TBS, **3b** or **d**), the ratio of **4eq** to the diastereomeric **4ax** was decreased (Entries 1 or 2 vs 3), and the same tendency was observed when the benzoyl (Bz) group was introduced as R^2 (Entry 2 vs 4). Existence of free hydroxy groups either at 2 or 6 positions led to the exclusive formation of **4eq** in AcOEt (Entries 3¹ and 4), which prompted us to employ a protic solvent, ethanol, to attain the higher proportion of **4eq** even when the totally protected form (**3b**) was employed (Entry 2 vs 5).

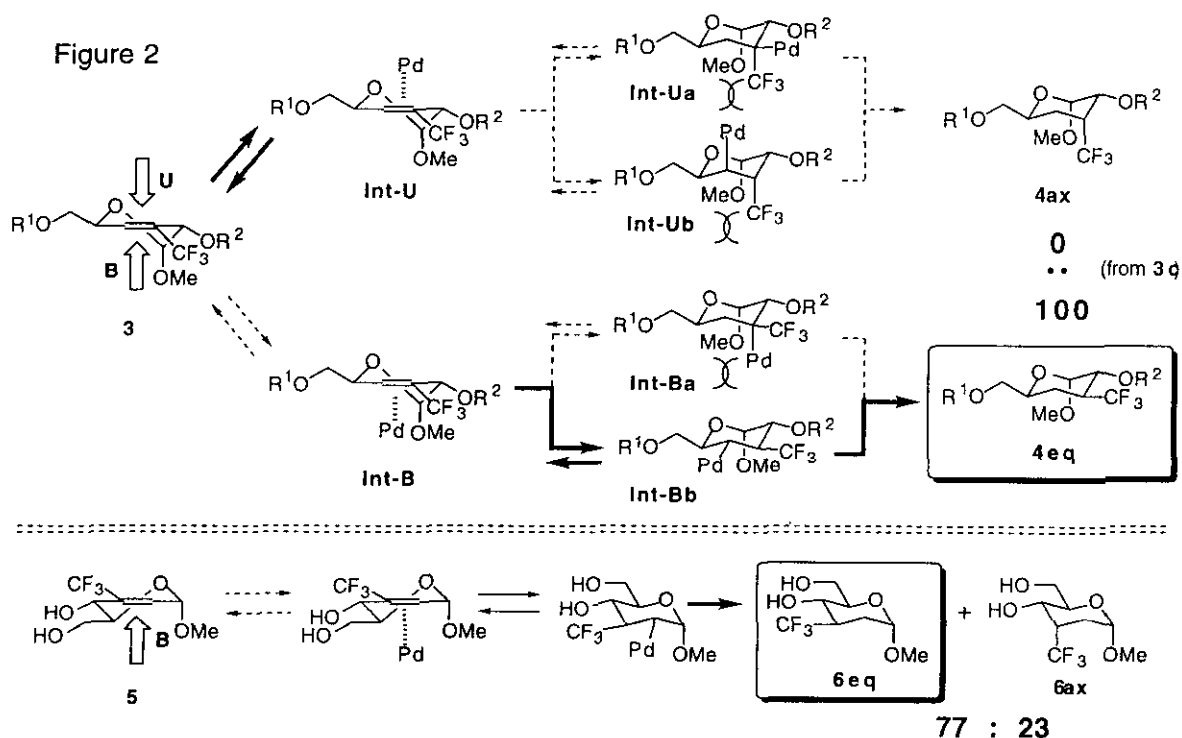
In general, this type of heterogeneous catalytic hydrogenation is considered to be a multistep equilibration sequence,³ and taking the previous report on the rate-controlling step⁴ into account, it is most likely that the observed stereoselectivity is the reflection of the thermodynamic stability difference of the intermediates just prior to departure of the Pd catalyst. In Figure 2 were described four possible intermediates (**Int-Ua**), (**Int-Ub**), (**Int-Ba**), and (**Int-Bb**) which expressed the approaching direction of a catalyst, upper (U) or bottom (B) face, followed by the site of the σ bonding carbon with Pd, at 3 (a) or 4 (b) position.

In the case of the preferred upper face selection, although the catalyst could be approached to **3** easier, the resultant intermediates (**Int-Ua**) and (**Int-Ub**) seem to be suffered from the significant 1,3-diaxial interaction between the methoxy and CF_3 groups, and consequently these paths are considered to afford **4ax** with great difficulty. On the other hand, interaction of a Pd catalyst from the hindered bottom face of **3** yielded either **Int-Ba** or **Int-Bb**. In spite of the unfavorable steric repulsion of **Int-Ba**, all the substituents of **Int-Bb** were arranged favorably in view of steric hindrance as well as electrostatic

Table 1. Hydrogenation of *endo*-Olefin (**3**)

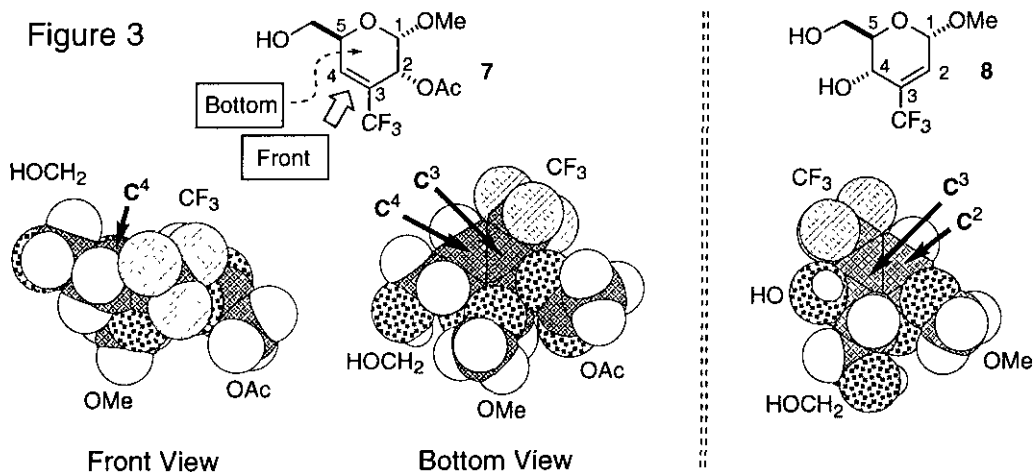


| Entry | Substrate | R^1 | R^2 | Solvent | Ratio by ^{19}F NMR | |
|-------|-----------|-------|-------|---------|-----------------------|------------|
| | | | | | 4eq | 4ax |
| 1 | 3a | Tr | Bz | AcOEt | 80 | 20 |
| 2 | 3b | TBS | Bz | AcOEt | 82 | 18 |
| 3 | 3c | H | Bz | AcOEt | 100 | 0 |
| 4 | 3d | TBS | H | AcOEt | 94 | 6 |
| 5 | 3b | TBS | Bz | EtOH | 97 | 3 |



interaction, allowing us to expect the smooth formation of the product (**4eq**). Considering the equilibrating pathways of this reaction possibly in a subtle energetic balance, difference between two equilibrating conditions **Int-B** ↔ **3** and **Int-U** ↔ **Int-Ua** (or **Ub**) would be the actual determinant of the present selectivity and the former is more favorable than the latter from the experimental results. The stereoselectivity of **5** would be also explained in the same manner (only the main path was depicted in Figure 2).

The present "unusual" facial selectivity was understood as discussed above, but how can we explain the substituent effect shown in Table 1? For obtaining detailed MO information, we investigated the semiempirical MOPAC calculations⁵ using compounds (**7**) and (**8**) with slight modification for **3c** and **5**, respectively, and the most stable conformations were described in Figure 3 as their CPK models. We also calculated 3,3,3-trifluoropropene $\text{CF}_3\text{-C}^{\text{a}}\text{H}=\text{C}^{\text{b}}\text{H}_2$ (the partial structures of both **7** and **8**) by Gaussian 92 (HF/6-31G*) software⁶ and it was proved that charges (C^{a} : -0.35, C^{b} : -0.34) as well as $2p_z$ orbital coefficients of LUMO (C^{a} : -0.35, C^{b} : 0.36) at both olefinic carbons were basically identical. Thus, we concluded that the regiochemistry of the reaction between a catalyst ("Pd-H") and CF_3 -containing olefins would be governed merely by the steric requirement to produce the Pd-C⁴ and H-C³ bonds rather than the opposite pairs in consideration of the bulkiness of a CF_3 group, already reported to be at least equivalent to a nonfluorinated isopropyl group.⁷ The "Front View" of **7** in Figure 3 indicated the conformational resemblance to its prototype (**3**) and the wide space around the upper olefinic face as shown in Figure 2, and vacancy around the C⁴ carbon atom is clearly observed in the "Bottom View". However, introduction of a protective group such as TBS or Tr moieties at 6 position should cause more or less the steric congestion and thus increase the importance of **Int-U** ↔ **Int-Ua** (or **Ub**) equilibration relative to **Int-B** ↔ **3**,



leading to the formation of the minor product (**4ax**). The role of an acyl group at 2-*O* position would be understood in an analogous manner. However, the CPK model of **8** demonstrates that the possible reaction site of **8** with 'Pd', C², is encumbered by the neighboring methoxy group, which would allow the more chance of the opposite face selection to decrease the ratio of **6eq** to the diastereomeric **6ax**.

As shown above, we have prepared in the highly stereoselective formation of 3-deoxy-3-*C*-trifluoromethylated carbohydrates *via* Pd-catalyzed hydrogenation, which was successfully explained⁸ by qualitative comparison of the equilibrating reaction pathways as well as the MO calculations.

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