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# Asymmetric Reduction of 2-Fluoro-2-(trifluoromethyl)-3-hydroxy Ketones with Lithium Aluminum Hydride or Diisobutylaluminum Hydride. Highly Stereoselective Synthesis of 2-Fluoro-2-(trifluoromethyl)-1,3-diols

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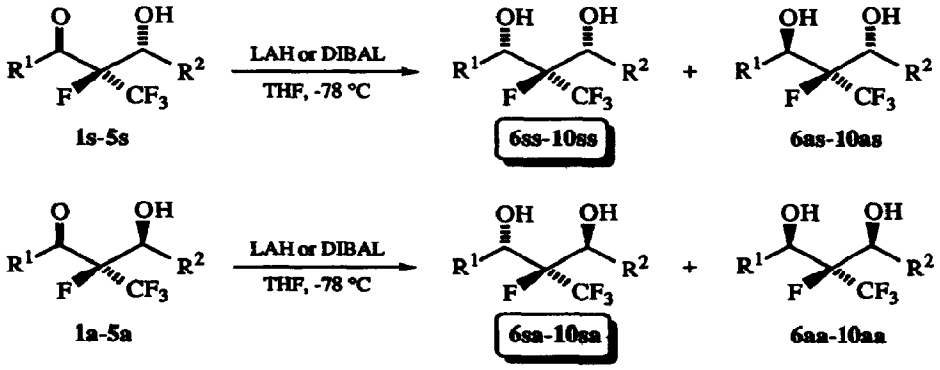
**Abstract:** The syn and anti isomers of 2-fluoro-2-(trifluoromethyl)-3-hydroxy ketones are reduced in a highly 1,2-syn diastereoselective manner with lithium aluminum hydride or diisobutylaluminum hydride in tetrahydrofuran at -78 °C, affording 1,2-*syn*-2,3-*syn*- and 1,2-*syn*-2,3-*anti*-2-fluoro-2-(trifluoromethyl)-1,3-diols, respectively, in excellent yields. High 1,2-syn stereoselectivity in the reduction can be ascribed to the presence of the 2-trifluoromethyl substituent.

Much attention has consistently been denoted to the stereoselective reduction of 3-hydroxy ketones to 1,3-diols because the reaction of this type is one of the most important transformations in constructing a variety of biologically active natural compounds, in which the 1,3-dioxygenated fragments are frequently found. Although a number of methods for such reductions have hitherto been accumulated in the literature,[2] their applications to fluorinated counterparts do not necessarily lead to satisfactory results[3] and hence there still exists need for new promising approaches to fluorine-containing 1,3-diol systems. Therefore, it is of great significance to develop an effective method for the stereoselective preparation of these compounds.

In this communication are disclosed asymmetric reductions of the syn and anti isomers of 2-fluoro-2-(trifluoromethyl)-3-hydroxy ketones (**1-5**) with lithium aluminum hydride (LAH) or diisobutylaluminum hydride (DIBAL), which take place in a highly 1,2-syn diastereoselective fashion irrespective of the stereochemistry of the β carbon (C-3) to give 1,2-*syn*-2,3-*syn*- (**6ss-10ss**) and 1,2-*syn*-2,3-*anti*-2-fluoro-2-(trifluoromethyl)-1,3-diols (**6sa-10sa**), respectively, in good to excellent yields. The present reactions provide a new simple and efficient method for the synthesis of stereochemically defined trifluoromethyl-carrying diols which are difficult otherwise to prepare.




The starting 3-hydroxy ketones **1-5** were prepared according to our recently reported method[4] and each diastereoisomer of **1-5** could easily be separated by column chromatography on silica gel (hexane–ethyl acetate).

**Table 1.** Reduction of 3-Hydroxy Ketones **1-5** with LAH or DIBAL[a]

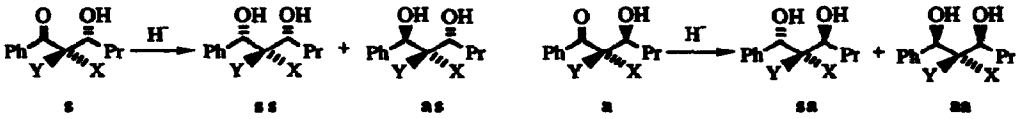
| Entry | $R^1$ | $R^2$ | | Reductant (equiv) | Yield/%[b] | Isomer ratio[c] |
|---|---|---|---|---|---|---|
| 1 | Ph | $CH_3(CH_2)_2$ | [1s] | LAH (3) | 77 | **6ss** : **6as** = 99 : 1 |
| 2 | | | [1s] | DIBAL (3) | 83 | **6ss** : **6as** = 99 : 1 |
| 3 | | | [1a] | LAH (3) | 83 | **6sa** : **6aa** = 95 : 5 |
| 4 | | | [1a] | DIBAL (3) | 92 | **6sa** : **6aa** = 99 : 1 |
| 5 | Ph | Ph | [2s] | LAH (3) | 92 | **7ss** : **7as** = 99 : 1 |
| 6 | | | [2s] | DIBAL (3) | 87 | **7ss** : **7as** = 99 : 1 |
| 7 | | | [2a] | LAH (3) | 84 | **7sa** : **7aa** = 92 : 8 |
| 8 | | | [2a] | DIBAL (3) | 78 | **7sa** : **7aa** = 99 : 1 |
| 9 | $CH_3(CH_2)_5$ | $CH_3(CH_2)_5$ | [3s] | LAH (3) | 80 | **8ss** : **8as** = 94 : 6 |
| 10 | | | [3s] | DIBAL (4) | 84 | **8ss** : **8as** = 98 : 2 |
| 11 | | | [3a] | LAH (3) | 77 | **8sa** : **8aa** = 87 : 13 |
| 12 | $CH_3(CH_2)_5$ | (*E*)-$CH_3CH$=CH | [4s] | LAH (3) | 90 | **9ss** : **9as** = 93 : 7 |
| 13 | | | [4a] | LAH (3) | 89 | **9sa** : **9aa** = 90 : 10 |
| 14 | $CH_3(CH_2)_5$ | Ph | [5s] | LAH (3) | 83 | **10ss** : **10as** = 90 : 10 |
| 15 | | | [5s] | DIBAL (4) | –[d] | **10ss** : **10as** = 99 : 1 |
| 16 | | | [5s] | DIBAL (5) | 92[e] | **10ss** : **10as** = 99 : 1 |
| 17 | | | [5a] | LAH (3) | 99 | **10sa** : **10aa** = 83 : 17 |
| 18 | | | [5a] | DIBAL (4) | 0[f] | —— |
| 19 | | | [5a] | DIBAL (5) | 99[e] | **10sa** : **10aa** = 48 : 52 |

a) Performed at -78 °C for 3 h. b) Yields refer to analytically pure products isolated as a diastereomeric mixture. c) Measured by $^{19}F$ NMR analysis of crude products. d) Not determined but an 80% conversion was confirmed. e) Carried out at room temperature. f) The starting ketone **5a** was recovered quantitatively.

The procedure for the reduction of 2,3-*syn*-2-fluoro-3-hydroxy-1-phenyl-2-(trifluoromethyl)-1-hexanone (**1s**) with DIBAL (Entry 2) is typical. To a solution of **1s** in tetrahydrofuran was added dropwise a 1.0 *M* hexane solution of DIBAL (3 equiv) at -78 °C. After being stirred for 3 h at -78°C, the reaction mixture was hydrolyzed with a cold 20% HCl solution and extracted with ether. The ethereal extracts were dried over $Na_2SO_4$ followed by concentration *in vacuo* to leave an oily residue, which was chromatographed on a silica-gel column (dichloromethane–ether) to give isomerically pure 1,2-*syn*-2,3-*syn*-2-fluoro-1-phenyl-2-(trifluoromethyl)-1,3-hexanediol (**6ss**) (83%).[5] The isomer distribution of the product was determined by $^{19}F$ NMR prior to isolation. The results of other reactions are summarized in Table 1.

As shown in Table 1, 3-hydroxy ketones **1-5** employed were nicely reduced either with LAH or with DIBAL stereoselectively (except for Entry 19) to afford the corresponding 2-fluoro-2-(trifluoromethyl)-1,3-diols **6-10** in good to excellent yields. The reductions with DIBAL were slightly more selective than those with LAH (Entries 3 and 4, 7 and 8, 9 and 10, 14 and 15). It should be noted that even use of LAH offered good levels of diastereoselection, in view of substantially low selectivity being observed for the reductions between fluorine-free 3-hydroxy ketones and LAH.[8] Of more significance is that both the syn **1s-5s** and anti isomers **1a-5a** underwent the reduction with high 1,2-syn stereoselectivity regardless of the configuration of the hydroxyl-bearing carbon (C-3), though the former exhibited a higher degree of stereoselectivity than the latter. These facts imply

**Table 2.** Reduction of 3-Hydroxy Ketones **11** and **12** with LAH or DIBAL[a]




| Entry | X | Y | | Reductant | Yield/%[b] | Isomer ratio[c] |
|---|---|---|---|---|---|---|
| 20 | $CH_3$ | F | [11s] | LAH | 99 | **13ss** : **13as** = 67 : 33 |
| 21 | | | [11s] | DIBAL | 84 | **13ss** : **13as** = 91 : 9 |
| 22 | | | [11a] | LAH | 95 | **13sa** : **13aa** = 22 : 78 |
| 23 | | | [11a] | DIBAL | 97 | **13sa** : **13aa** = 69 : 31 |
| 24 | $CH_3$ | H | [12s] | LAH | 91 | **14ss** : **14as** = 84 : 16 |
| 25 | | | [12s] | DIBAL | 83 | **14ss** : **14as** = 99 : 1 |
| 26 | | | [12a] | LAH | 88 | **14sa** : **14aa** = 61 : 39 |
| 27 | | | [12a] | DIBAL | 97 | **14sa** : **14aa** = 83 : 17 |

a) Conducted under similar conditions to those for the reduction of **1**. b) See footnote b in Table 1. c) See footnote c in Table 1.

that such stereoselection can be attributed to the stereochemistry of the α carbon (C-2) of **1-5**, on which the trifluoromethyl substituent is located. In order to ascertain the effect of this substituent on the stereochemistry of the reduction, 2-fluoro-3-hydroxy-2-methyl-1-phenyl-1-hexanone (**11**)[9] and a nonfluorinated counterpart, 3-hydroxy-2-methyl-1-phenyl-1-hexanone (**12**)[10] were subjected to the reduction with LAH or DIBAL under the same reaction conditions. As can be seen from Table 2, the reductions of **11** (Entries 20-23) as well as of **12** (Entries 24-27) were shown to occur with appreciably low diastereoselectivity compared with the reductions of **1** (Entries 1-4 in Table 1), and the monofluorinated 3-hydroxy ketone **11** was reduced less stereoselectively than the nonfluorinated ketone **12**. These results provide us with a strong suggestion that the 2-trifluoromethyl group plays a critical part in determining the stereochemical course of the reduction of **1**. The trifluoromethyl group, one of the most electronegative groups, is generally considered as bulky as the isopropyl or *t*-butyl group,[11] so that the differences in selectivity between these reductions are presumable to stem primarily from those in steric bulk between the trifluoromethyl and methyl groups.

The 1,2-syn stereoselectivity obtained in the present reductions of **1-5** may be explained as follows. The reductant LAH or DIBAL can first react with the hydroxyl goup of the starting diastereomeric ketone to give the corresponding ketone alkoxide, which participates in a six-membered chelation. The chelate species formed would exist in a pseudo chair conformation where the 2-trifluoromethyl group occupies an axial rather than equatorial position due to as much relief as possible of steric interactions, particularly eclipsing interactions with $R^1$ and $R^2$. Thus, the attack of hydride should take place from sterically less hindered side, that is the opposite side of the trifluoromethyl group, to result in the preferential formation of the 1,2-syn stereoisomer.

In conclusion, it was noted that 2-fluoro-2-(trifluoromethyl)-3-hydroxy ketones **1-5** were reduced in a highly stereoselective manner with common reducing agents such as LAH or DIBAL to give 1,2-*syn*-1,3-diols **6-10**. This method can serve as a synthetically useful route to trifluoromethylated 1,3-diols with defined configurations, in terms of simple manipulations, high stereoselectivity, and good yields of the products.

**References and Notes**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7. $^1$H NMR (200 MHz) data for the typical acetonides are as follows. Acetonide of **6ss**: δ 0.95-1.08 (m, 3H), 1.25-2.00 (m, 10H), 4.11 (dddq, $J$ = 10.0, 5.6, 2.3, 2.2 Hz, 1H), 5.09 (dq, $J$ = 8.0, 1.8 Hz, 1H), 7.32-7.55 (m, 5H); that of **6sa**: δ 1.00-1.15 (m, 3H), 1.42-1.90 (m, 10H), 4.09 (ddd, $J$ = 24.6, 8.8, 2.9 Hz, 1H), 5.03 (dq, $J$ = 15.8, 1.5 Hz, 1H), 7.38-7.60 (m, 5H); that of **7ss**: δ 1.46 (s, 3H), 1.50 (s, 3H), 5.35 (dq, $J$ = 7.9, 1.8 Hz, 2H), 7.33-7.63 (m, 10H); that of **7sa**: δ 1.55 (s, 3H), 1.60 (s, 3H), 5.26 (d, $J$ = 23.6 Hz, 1H), 5.30 (dq, $J$ = 15.7, 1.8 Hz, 1H), 7.33-7.60 (m, 10H).
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