Chemoenzymatic Enantiospecific Synthesis of a Fluorinated *myo*-Inositol Analogue

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INTRODUCTION

Inositol derivatives play important roles in biological systems.[1a-c] D-*myo*-Inositol 1,4,5-trisphosphate [Ins(1,4,5)P3] (**1**) is a major second messenger associated with many cellular signaling processes (**Figure 1**).[1a-c,2] Among other analogs, fluorinated inositols have been studied as biological probes for pathways involving cyclitol biotransformations.[2,3]

Herein, we describe an enantiospecific synthesis of 1L-(–)-4-deoxy-4-fluor-*myo*-inositol [(–)-**2**] *via* an enzymatic kinetic resolution approach (**Figure 1**).[2b]

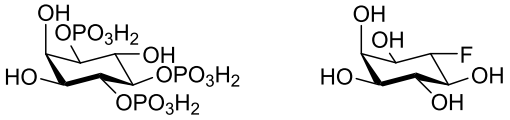
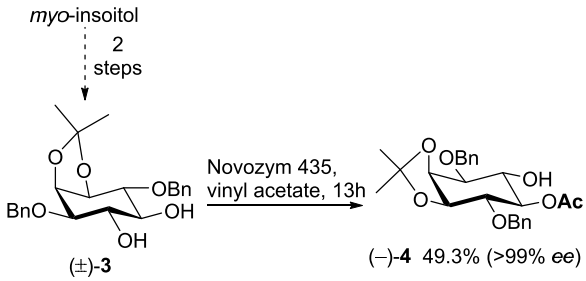


Figure 1. IP_3 and a fluorinated analogue of *myo*-inositol.

RESULTS AND DISCUSSION

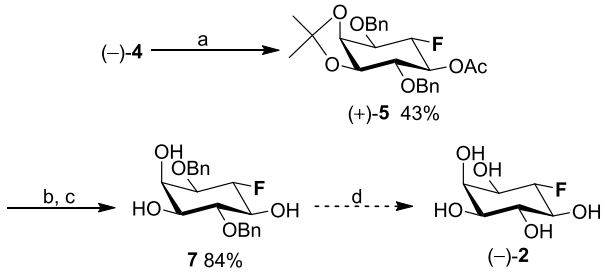
Recently, our group developed and optimized an efficient enzymatic resolution of diol (±)-**3** leading to (–)-**4**. (**Scheme 1**).[4a,b]



Scheme 1. Enzymatic resolution of monoacetate **3**.

Thus, we studied the deoxofluorination reaction of enantiopure (–)-**4** (**Scheme 2**).[5] Use of DAST in DCM (CH_2Cl_2) or toluene with DMAP (60°C) resulted in low yields of (+)-**5**. However, we found that a cleaner and faster reaction was achieved with DAST (5.0 equiv.) in excess (toluene, no base, r.t.) (under optimization). With XtalFluor-E in DCM, fluoride (+)-**5** was not formed. Analyses of 1D/2D H^1, C^{13} and F^{19}-NMR confirmed the formation of compound (+)-**5**, with retention of relative configuration.

After two successive hydrolyses, triol **7** was obtained in 84% overall yield. A straightforward catalytic hydrogenation catalyzed will provide the final target, (–)-**2.**



(a) DAST, PhMe, r.t., 1h; (b) NaOH 10%, MeOH, r.t., 30min, then Amberlite IR-120; (c) EtOH, H_2O (3 eq.), PTSA, 90ºC, 3h, then Et_3N; (d) H_2, Pd/C

Scheme 2. Synthesis of L-(–)-**2**.

CONCLUSION

The underdeveloped application of lipases to enantioselective synthesis of inositols proved fruitful. Following the necessary optimization of the deoxyfluorination, a practical and economical synthesis of L-(–)-**2** will become available.

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