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LETTERS

Novel Synthesis of Enantiomerically Pure Natural Inositols and Their Diastereomers

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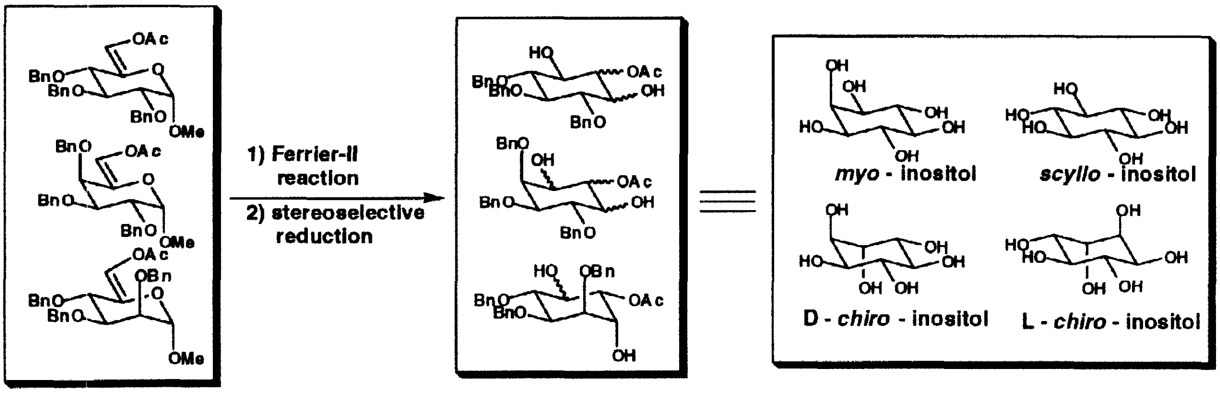
Abstract

A novel synthesis of all stereoisomers of natural inositols has been developed. The key strategy is the stereoselective reduction of substituted β-hydroxy cyclohexanones, which are prepared from a variety of 6-*O*-acetyl 5-enopyranosides via Ferrier-II reaction catalyzed by palladium chloride. The utility of this approach is demonstrated by the synthesis of D-*myo*-inositol 1,4,5-tris(phosphate)(IP$_3$).

Keywords: palladium and compounds; reduction; ring transformation; inositols

Various inositol polyphosphates and inositol phospholipids have been found to trigger many important biological processes.[1-14] Although knowledge concerning this phosphoinositide cell signaling system has been increasing in the past ten years, the chemical mechanisms whereby phosphoinositols mediate the cellular information are still obscure.

Scheme 1



For this reason, there are increasing demands for practical and efficient synthetic methods to prepare naturally occurring inositols and their analogues, including

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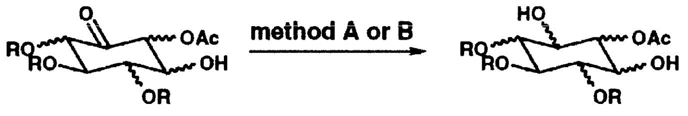
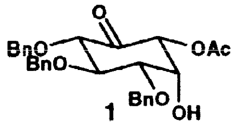
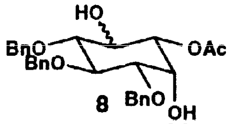
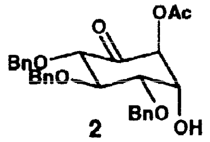
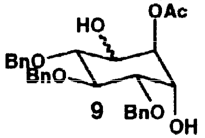
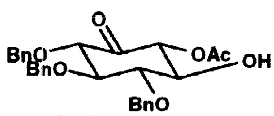
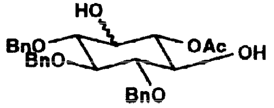
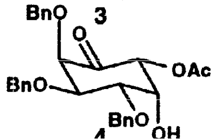
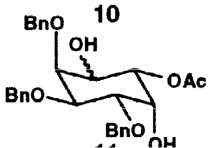
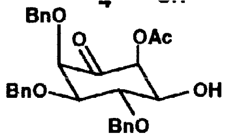
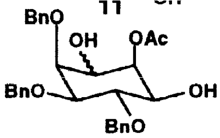
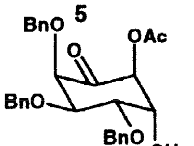
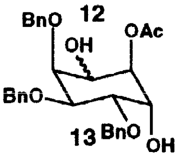
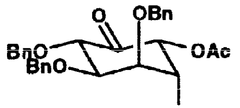
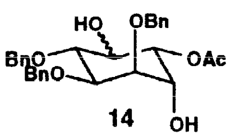
diastereomers. Here we report a novel synthesis of precursors for natural inositols (*myo*-inositol, *scyllo*-inositol, D-*chiro*-inositol and L-*chiro*-inositol) and their diastereomers starting with 6-*O*-acetyl-5-enopyranosides.

In the preceding paper, we described that Ferrier-II reaction of 6-*O*-acetyl-5-enopyranosides using a catalytic amount of palladium chloride provided a series of stereochemically defined penta-oxygenated cyclohexanones. [15]

Table 1



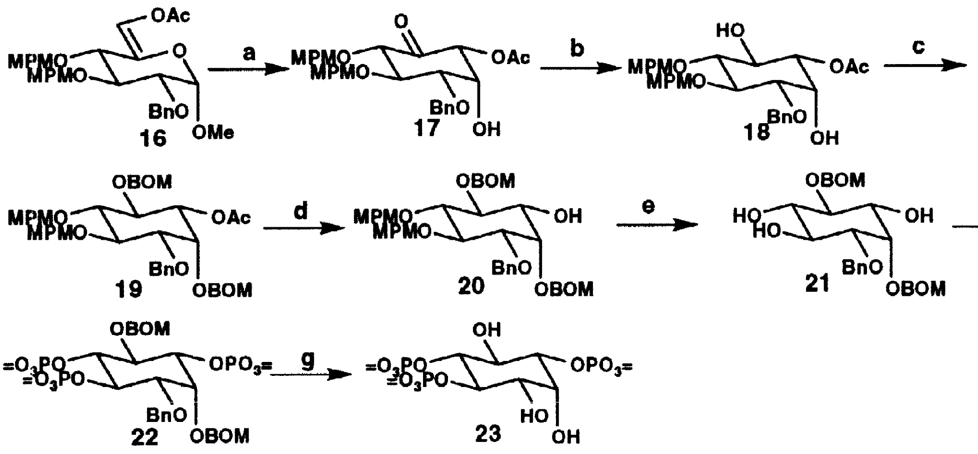
method A : $Me_4NHB(OAc)_3$ (5.0 eq), CH_3CN - AcOH
method B : $NaBH_4$ (1.5 eq), MeOH

Run	Substrtate	Method	Condition	Product	Yield	α : β[a]
1	 1	A B	-20 °C, 3 h 0 °C, 12 h	 8	84% 83%	< 1 : 99 > 99 : 1
2	 2	A B	0 °C, 1 h 0 °C, 0.5 h	 9	88% 84%	< 1 : 99 87 : 13
3	 3	A B	r.t., 24 h 0 °C, 0.5 h	 10	37% 86%	78 : 22 22 : 78
4	 4	A B	r.t., 24 h -78 °C, 0.5 h	 11	46% 90%	30 : 70 < 1 : 99
5	 5	A B	0 °C, 3h -78 °C, 0.5 h	 12	89% 88%	> 99 : 1 2 : 98
6	 6	A B	r.t., 48 h 0 °C, 0.5 h	 13	N. R. 96%	– : – <1 : 99
7	 7	A B	0 °C, 3h -40 °C, 0.5 h	 14	87% 92%	<1 : 99 98 : 2

[a] The assignment of the ratio was based on the ^1H NMR (400 MHz) analysis of the diastereomixtures.

We then focused on the stereoselective reduction of these β-hydroxycyclohexanones, which would satisfy the stereochemical requirements of all of the naturally observed inositols and their diastereomers. As shown in Table 1, the reduction of hydroxyketones **1**, **2**, **5** and **7** with $Me_4NBH(OAc)_3$ (method A) [16] provided *anti* diols in good yields with excellent diastereoselectivity (run 1, 2, 5 and 7). The intramolecular delivery of a hydride directed by the β-hydroxy group, as proposed by Evans, might lead to such a high diastereoselectivity. Unfortunately, hydroxyketones **3**, **4** and **6** were not reduced or yields were diminished, moreover, low diastereoselectivities were observed in this method. The comparison of the NMR spectra of these substrates suggests that the conformations of **3**, **4** and **6** differ significantly from those of **2**, **5** and **7**. These conformational changes may prevent the chelation of a hydroxy group with the reducing reagent. Reduction with $NaBH_4$ (method B) was also performed for comparison. As shown in Table 1, high diastereoselectivities were attained for all substrates tested. It should be pointed out that the stereochemical course of $NaBH_4$ reduction was complementary to that of $Me_4NBH(OAc)_3$ reduction. We speculate that a hydride attacked from the less hindered site of ketones because $NaBH_4$ could not coordinate to a hydroxy group. Overall, the set of reductions presented in Table 1 provided the eight stereoisomers of the inositols as a protected form. However, *cis*-inositol, which was the only one isomer not provided in Table 1, was easily derived from **8**.[18]

Scheme 2



Reagents and conditions: a) $PdCl_2$, dioxane-H_2O, 60 °C, 6 h, 53%; b) $Me_4NBH(OAc)_3$, AcOH-CH_3CN, r.t., 3 h, 81 %; c) BOMCl, *i*Pr_2NEt, $ClCH_2CH_2Cl$, reflux, 5 h, 78 %; d) NaOH, MeOH, 60 °C, r.t., 10 min, 81 %; e) DDQ, CH_2Cl_2-H_2O, r.t., 1 h, 80 %; f) (i) $(BnO)_2P(i\text{-}Pr_2N)$, tetrazole, CH_2Cl_2, r.t., 12 h, (ii) *m*CPBA, Na_2HPO_4, r.t., 1 h, 89%; g) H_2, $Pd(OH)_2/C$, MeOH, r.t., 12 h, 90 %.

The method described above enabled us to synthesize D-*myo*-inositol 1,4,5-tris(phosphate)(IP_3) [4] in enantiomerically pure form. Scheme 2 shows our synthetic route. Ferrier-II reaction of **16** in the presence of a catalytic amount of palladium chloride furnished the β-hydroxy ketone **17** with the desired stereoselectivity in 53% isolated yield. Stereoselective reduction with $Me_4NBH(OAc)_3$ provided the *anti* diol **18** in good yield. BOM groups were readily introduced to diols **18** in 78% yield with BOMCl and diisopropylethylamine. Sequential deacetylation by basic methanolysis and deprotection of the MPM groups with DDQ in wet CH_2Cl_2 afforded triol **21**. Treatment of triol **21** with bis(benzyloxy)(*N,N*-diisopropylamino)phosphine in the presence of tetrazole gave the fully protected IP_3 derivative **22**. Finally, hydrogenolysis of the benzyl groups and BOM groups provided the optically active D-*myo*-inositol 1,4,5-tris(phosphate)(IP_3)**23** in 90% yield. [19]

In summary, naturally observed inositols and all of their diastereoisomers have been effectively synthesized as fully protected forms. As we have presented above, this approach will be widely applicable to the synthesis of all natural and unnatural analogues of phosphoinositols. The biological uses of these derivatives will be reported in due course.

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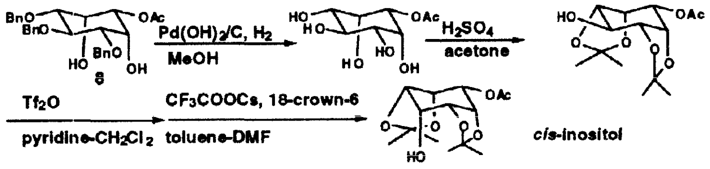
[17] **16** was prepared in 9 steps from α-D-Methyl glucoside.
[18] *cis*-inositol was prepared in 4 steps from **8**.



[19] The synthetic material was identical in all respects with a sample of the natural product.