Synthesis of Branched-chain D-*myo*-Inositols using the [3,3]Sigmatropic Claisen Rearrangement

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A new and efficient synthesis of branched-chain cyclitols and their congeners utilizing a stereospecific Claisen rearrangement is reported.

Almost twenty years have passed since Michell's suggestion[1] that the phosphoinositide cascade is associated with cellular Ca^{2+} mobilization. Subsequently, Berride *et al.*[2] and Nishizuka[3] identified D-*myo*-inositol 1,4,5-trisphosphate INS[(1,4,5)P_3] and *sn*-1,2-diacylglycerol (DAG) as second messengers produced by phospholipase C (PLC) catalysed hydrolysis of the minor membrane lipid phosphatidylinositol 4,5-bisphosphate. INS[(1,4,5)P_3] releases Ca^{2+} from intracellular and extracellular stores and DAG is an activator of protein kinase C (PKC). These messenger systems control a vast number of important signal transduction processes.

Numerous syntheses of INS[(1,4,5)P_3] and other inositol phosphates have been reported.[4] Unfortunately, the majority of these contributions result in racemic mixtures and no general synthetic approaches for the preparation of enantiomerically pure inositols and branched-chain cyclitols have been described.

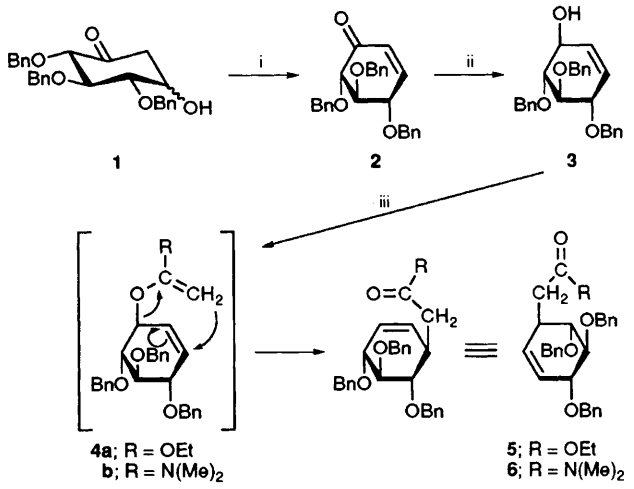
In an effort to develop *myo*-inositol phosphate molecules related to metabolites of the phosphoinositide cycle that might find therapeutic applications, we became interested in the preparation of branched-chain *myo*-inositols and their phosphates.

We report in this communication the synthesis of enantiomerically pure branched-chain *myo*-inositols and their phosphate esters in which the pivotal 1-hydroxy group has been replaced by metabolically stable lipophilic isosteres with the same stereochemistry as *myo*-inositol.

It is interesting to note that the 1-position of *myo*-inositol-1-phosphate is the primary site of action of lithium ions in the treatment of manic-depression and replacements of 1-*O*-phosphate in INS[(1,4,5)P_3] with lipophilic groups give products which still interact and bind with IP_3 receptors.[5]

Conduritol **3** was chosen as a convenient starting material for the synthesis of branched-chain *myo*-inositols (Scheme 1). We initially anticipated that the target molecules could be obtained by a Claisen rearrangement from conduritol **3**. The latter {(m.p. 116 °C; $[\alpha]_D^{25}$ = + 115 (*c* 1.2, $CHCl_3$)} was readily prepared in 90% yield from inosose[6] **1** by a two-step high yielding procedure *via* the stereoselective reduction of the known α,β-unsaturated ketone[7] **2** using sodium borohydride and cerium trichloride[8] ($CeCl_3$, 7 H_2O) in methanol.

When **3** was heated in diglyme with either triethylorthoacetate and a catalytic amount of propionic acid or *N*,*N*-dimethylacetamide dimethyl acetal at 160 °C for 4 h the intermediates **4a** and **4b** underwent a [3,3]sigmatropic rearrangement yielding exclusively the unsaturated branched-chain cyclitols **5** as an oil (70%) {$[\alpha]_D^{25}$ = −92 (*c* 0.6, $CHCl_3$)} and crystalline **6** (80%) {(m.p., 62 °C) $[\alpha]_D^{25}$ = −123 (*c* 2, $CHCl_3$)}. Although the original chiral centre is destroyed in the rearrangement (4a, 4b, 5 and 6), it reappears two carbon atoms away in the



Scheme 1 *Reagents*: i, MsCl, DMAP; ii, $CeCl_3$, $NaBH_4$; iii, $MeC(OMe)_2NMe_2$ or $MeC(OEt)_3$

allylic position. One of the useful features of the reaction is its ability to transmit chirality along a carbon chain, a well-known phenomenon in natural product chemistry.[9] To our knowledge, there has been no report of this strategy to produce the title compounds from conduritols. The presence of the double bond and the functional groups in **5** made possible the synthesis of a variety of branched-chain *myo*-inositols in a regio- and stereo-selective manner as shown in Scheme 2.

Thus, treatment of **5** with a catalytic amount of osmium tetroxide (OsO_4) in acetone–water, (2.5 : 1) and *N*-methylmorpholine-*N*-oxide resulted in the production of a single diol **7** {m.p. 139–141 °C; $[\alpha]_D^{25} = +8$ (*c* 1.8, CH_2Cl_2)} in 80% yield. Selective benzoylation using benzoyl chloride–pyridine provided the mono-benzoate **8** {m.p. 84–86 °C; $[\alpha]_D^{25} = 28$ (*c* 0.29, $CHCl_3$)} in 92% yield. Its *myo* configuration was unequivocally determined by ^1H NMR decoupling experiments.

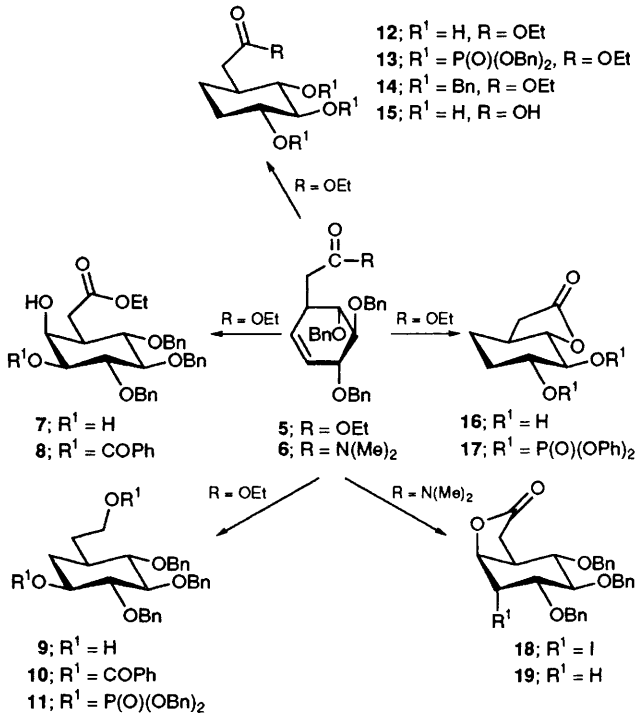
Hydroboration of **5** with an excess of borane–tetrahydrofuran complex (1 mol dm^{-3}) afforded the crystalline diol **9** in 80% yield {m.p. 83–85 °C; $[\alpha]_D^{25} = +10$ (*c* 0.5, CH_2Cl_2)} with high regio- and stereo-selectivity. The structure of **9** was determined from the ^1H NMR spectrum of its dibenzoate **10** {$[\alpha]_D^{25} = +6$ (*c* 0.18, CH_2Cl_2)}.

Catalytic reduction of the double bond in **5** with concomitant hydrogenolysis of the benzyl groups using Pd/C 10% in ethanol led to the triol **12**.

For the preparation of 2,3-dideoxylactone **16** having a lactone substituted at positions 1 and 6, the double bond in **5** was first cleanly reduced with a catalytic amount of PtO_2 in ethanol to give the crystalline **14** (m.p. 51 °C; $[\alpha]_D^{25} = -13.4$ (*c* 0.56, $CHCl_3$)} in 75% yield. Hydrolysis of the ester function in **14** followed by hydrogenolysis of the benzyl groups furnished the acid **15** (80%). The latter was transformed into the corresponding lactone **16** by means of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide in pyridine.

Compound **6** was used as starting material for the synthesis of lactone **19**. Thus, treatment of **6** with iodine[10] in tetrahydrofuran–water (1 : 1) at 0 °C afforded in 60% yield the crystalline iodolactone **18** {m.p. 136 °C; $[\alpha]_D^{25} = -23$ (*c* 2.24, $CHCl_3$)}. De-iodination of **18** with tributyltin hydride and AIBN in refluxing toluene gave the crystalline lactone **19** {m.p. 72 °C; $[\alpha]_D^{25} = -4$ (*c* 1.32, $CHCl_3$)} (70%).

The diol **9** and the triol **12** were phosphorylated with the phosphite triester method using *N,N*-diisopropyldibenzyl phosphoramidite[11] in the presence of 1*H*-tetrazole in acetonitrile followed by oxidation with *tert*-butylhydroperoxide giving the protected diphosphate **11** {m.p. 40–42 °C; $[\alpha]_D^{25} = -2$ (*c* 0.92, CH_2Cl_2)} and the triphosphate **13** {$[\alpha]_D^{25} = -7$ (*c* 1.96, CH_2Cl_2)}, respectively.



Scheme 2

Finally, phosphorylation of **16** with diphenylchlorophosphate[12] and dimethylaminopyridine (DMAP) in CH_2Cl_2 afforded the crystalline diphenylphosphate lactone† **17** {m.p. 108–110 °C; $[\alpha]_D^{25} = +15$ (*c* 1.4, CH_2Cl_2)}.

This communication shows that the branched-chain D-*myo*-inositols and their congeners can be synthesised stereoselectively in a suitably protected form. Deprotection of the phosphates will furnish biologically interesting D-*myo*-inositol derivatives.

Received, 22nd March 1993; Com. 3/01647A

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† All new compounds were characterised by NMR spectroscopy (200 MHz), MS, IR spectroscopy, micro-analysis, and optical rotation.