

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

Sophie Augy-Dorey,^a Derek H. R. Barton,^b Stephen D. Géro,^a Béatrice Quiclet-Sire*^a and Isabelle Sagnard^a

^a Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif-sur-Yvette, Cedex, France

^b Department of Chemistry, Texas A&M University, College Station, Texas 77843, USA

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 suggestion¹ that the phosphoinositide cascade is associated with cellular Ca²⁺ mobilization. Subsequently, Berridge *et al.*² and Nishizuka³ identified D-*myo*-inositol 1,4,5-trisphosphate INS[(1,4,5)P₃] 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)P₃] releases Ca²⁺ 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)P₃] 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.

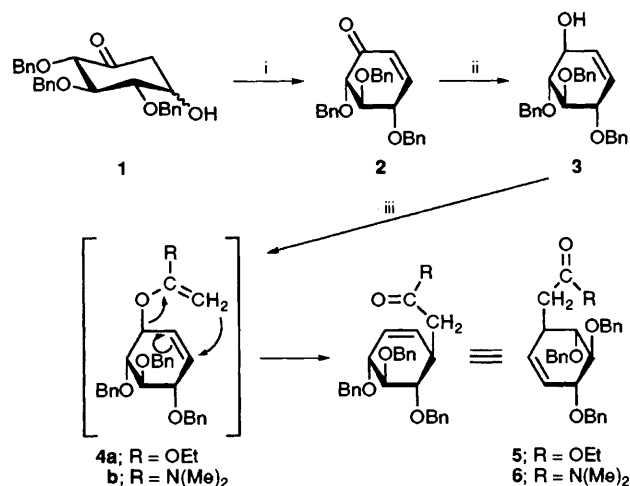
We report in this communication the synthesis of enantiomerically pure branched-chain *myo*-inositols and their phosphate esters in which the pivotal 1-hydroxy group has

been replaced by metabolically stable lipophilic isosteres with the same stereochemistry as *myo*-inositol.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)P₃] with lipophilic groups give products which still interact and bind with IP₃ 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; [α]_D²⁵ = +115 (c 1.2, CHCl₃)) was readily prepared in 90% yield from inosose⁶ **1** by a two-step high yielding procedure *via* the stereoselective reduction of the known α,β-unsaturated ketone⁷ **2** using sodium borohydride and cerium trichloride⁸ (CeCl₃, 7 H₂O) 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%) {[α]_D²⁵ = -92 (c 0.6, CHCl₃)} and crystalline **6** (80%) (m.p., 62 °C) [α]_D²⁵ = -123 (c 2, CHCl₃). 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, CeCl₃, NaBH₄; iii, MeC(OMe)₂NMe₂ 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 (OsO₄) 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; [α]_D²⁵ = +8 (c 1.8, CH₂Cl₂)} in 80% yield. Selective benzylation using benzoyl chloride-pyridine provided the mono-benzoate **8** {m.p. 84–86 °C; [α]_D²⁵ = 28 (c 0.29, CHCl₃)} 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; [α]_D²⁵ = +10 (c 0.5, CH₂Cl₂)} with high regio- and stereo-selectivity. The structure of **9** was determined from the ¹H NMR spectrum of its dibenzoate **10** {[α]_D²⁵ = +6 (c 0.18, CH₂Cl₂)}.

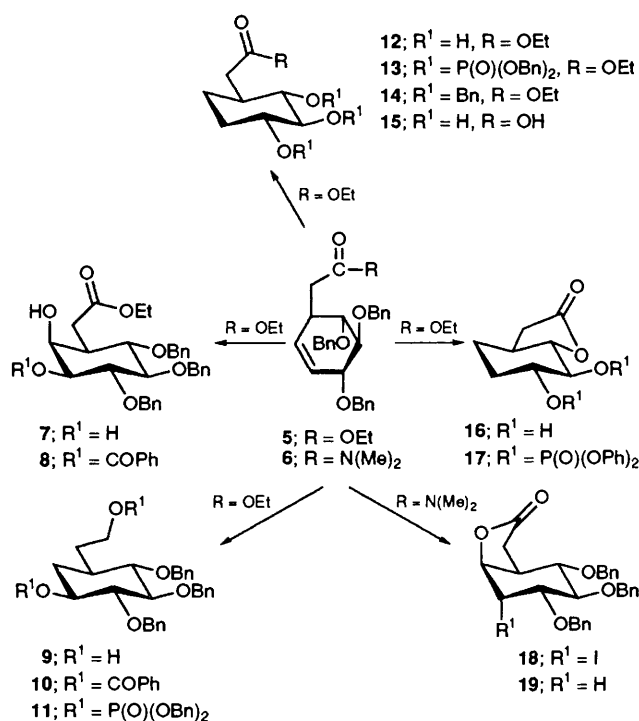
Catalytic reduction of the double bond in **5** with concomitant hydrogenolysis of the benzyl groups using Pd/C 10% in ethanol led to the triol **12**.

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 PtO₂ in ethanol to give the crystalline **14** (m.p. 51 °C; [α]_D²⁵ = -13.4 (c 0.56, CHCl₃)} 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 iodine¹⁰ in tetrahydrofuran-water (1:1) at 0 °C afforded in 60% yield the crystalline iodolactone **18** {m.p. 136 °C; [α]_D²⁵ = -23 (c 2.24, CHCl₃)}.

De-iodination of **18** with tributyltin hydride and AIBN in refluxing toluene gave the crystalline lactone **19** {m.p. 72 °C; [α]_D²⁵ = -4 (c 1.32, CHCl₃)} (70%).

The diol **9** and the triol **12** were phosphorylated with the phosphite triester method using *N,N*-diisopropylidibenzyl phosphoramidite¹¹ 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; [α]_D²⁵ = -2 (c 0.92, CH₂Cl₂)} and the triphosphate **13** {[α]_D²⁵ = -7 (c 1.96, CH₂Cl₂)}, respectively.



Scheme 2

Finally, phosphorylation of **16** with diphenylchlorophosphate¹² and dimethylaminopyridine (DMAP) in CH₂Cl₂ afforded the crystalline diphenylphosphate lactone† **17** {m.p. 108–110 °C; [α]_D²⁵ = +15 (c 1.4, CH₂Cl₂)}.

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. 3101647A

References

- R. H. Mitchell, *Biochim. Biophys. Acta*, 1975, **415**, 81.
- H. Streb, R. F. Irvine, M. J. Berridge and I. Schulz, *Nature*, 1983, **312**, 374.
- Y. Nishizuka, *Nature*, 1984, **308**, 693; Y. Nishizuka, *Science*, 1992, **258**, 607.
- D. C. Billington, *The Inositol Phosphates: Chemical Synthesis and Biological Significance*, 1993, VCH and references therein.
- T. McInally, I. Millichip, A. C. Tinker, C. Hallam, A. Kirk and A. Wallace, posters presented at the *11th International Symposium on Medicinal Chemistry*, Jerusalem, 1990. Copies available from T. McInally, Department of Medicinal Chemistry, Fisons plc, Bakewell Road, Loughborough, Leicestershire, UK LE11 0RH.
- D. Semeria, M. Phillippe, J. M. Delaumeny, A. M. Sepulchre and S. D. Géro, *Synthesis*, 1983, **7**, 10.
- M. Phillippe, PhD Thesis, University Paris XI, 1984.
- J. L. Luche, A. L. Gemal, *J. Am. Chem. Soc.*, 1979, **101**, 5848.
- F. E. Ziegler, *Acc. Chem. Res.*, 1977, **10**, 227; P. A. Bartlett, *Tetrahedron*, 1980, **36**, 3.
- E. J. Corey, M. Shibasaki and J. Knolle, *Tetrahedron Lett.*, 1977, **19**, 1625.
- T. W. Bannwarth and A. Trzeciak, *Helv. Chim. Acta*, 1987, **70**, 175.
- J. P. Vacca, S. J. De Solms and J. R. Huff, *J. Am. Chem. Soc.*, 1987, **109**, 3478.

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