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Carbohydrate Research 307 (1998) 163–165

Note

New conditions for the synthesis of *scyllo*-inositol starting from *myo*-inositol

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Received 27 October 1997; accepted 18 December 1997

Abstract

Equilibration of *myo*-inositol by Raney nickel in water has been reconsidered on a preparative scale. An efficient separation of *scyllo*-inositol by orthoacetate derivatization of the components of the crude mixture is proposed which gives the free *scyllo*-inositol in good yield.

Keywords: *Scyllo*-inositol; *Myo*-inositol; Catalytic equilibration

Scyllo-inositol is rare and expensive. One of the best ways to prepare this cyclitol depends on an enzymic synthesis (*Acetobacter suboxydans*) of the 2,4,6/3,5-pentahydroxycyclohexanone (*meso*-2-inosose), described by Kluyver [1] and starting from *myo*-inositol. This product has been shown to be reduced by sodium amalgam in acidic medium to a mixture of inositols containing 33% of *scyllo*-inositol [2] which has been separated from the mixture in acetylated form due to its very low solubility in alcohol. The *meso*-2-inosose was also reduced to approximately the same proportions of inositols by sodium borohydride [3]. However in either case the overall yield is poor, the total time of synthesis is long and the method used to purify the product gives *scyllo*-inositol only as a derivative. Other syntheses starting from hexahydroxybenzene [4] or conduritol B gave less than 5% of *scyllo*-inositol [5]. Sasaki has described experimental conditions for separations of inositol mixtures on Dowex 1 resin [6] and by Ca^{2+} selective complexation with an HPLC [7,8] device. Phillips has also partially resolved inositol mixtures on a silica (Microsil) HPLC column [9]. We report here an improvement of the synthesis and a very simple and efficient way for the separation the free *scyllo*-inositol on the gram scale based on the very low solubility of *scyllo*-inositol in water compared to the surprisingly higher solubility of *myo*-inositol orthoacetate in the same solvent. In the experimental conditions described underneath (temperature below 100 °C) neither mono nor bis orthoacetate of *scyllo*-inositol was produced. This was not unexpected since Vogl et al. have shown that any formation of orthoesters could not be observed at 150–200 °C with either triethyl orthoacetate or triethyl orthoformate [10].

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0008-6215/98/$19.00
PII S0008-6215(98)00003-2

Much work has been done on equilibration of diastereoisomers of sugars [11] or cyclitols [6,12] by Raney nickel in water or deuterium oxide. The mechanism of this equilibration is not yet completely understood but it is clear however that thermodynamically stable diastereoisomers are favored in the resulting mixture provided that equilibrium has been reached [13].

1. Experimental

In the first step *myo*-inositol (20 g, 111 mmol) was dissolved in distilled water (250 mL) and refluxed with Raney nickel (30 g) (Fluka 83440). The solution was approximately at pH 10. After 24 h the reaction medium was filtered and the clear filtrate was concentrated to 10% by volume. The mixture of inositols was precipitated by ethanol addition at 80 °C. The ^{1}H NMR spectrum (Fig. 1(a)) of the crude product revealed 20–30% (depending on experiment) of *scyllo*-inositol as well as unreacted *myo*-inositol. The total recovered crude material was 16 g.

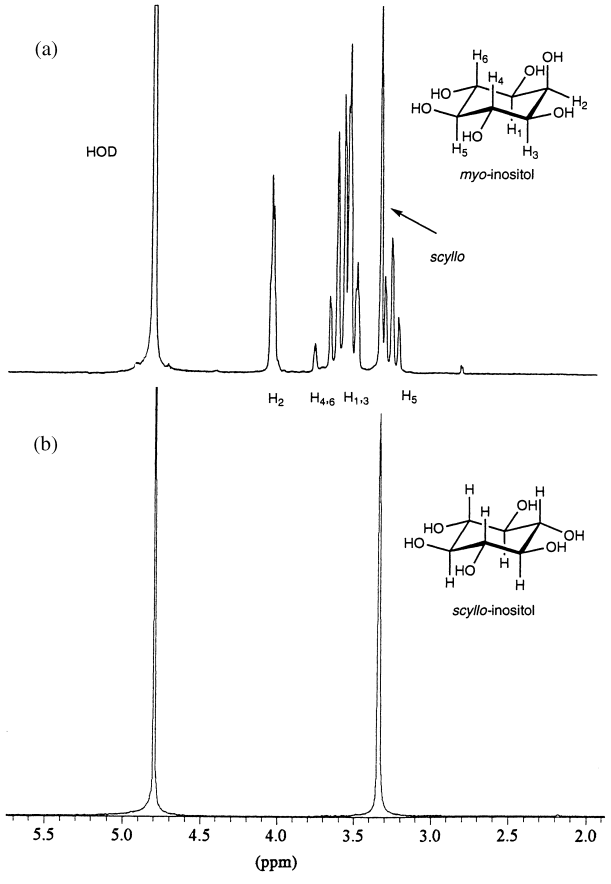

Fig. 1. (a) ^{1}H NMR spectrum of the crude product resulting from epimerization by Raney nickel. Protons are referred to the usual nomenclature of the inositols; (b) ^{1}H NMR spectrum of crystalline *scyllo*-inositol showing only one signal due to the presence of a C_6 symmetry axis for the molecule. Small pics at 2.8 and 3.77 ppm in the spectrum of the crude product are respectively attributable to traces of quebractitols and other inositols.

In the second step the crude product obtained was dissolved in anhydrous DMF (100 mL) and stirred with triethylorthoacetate (60 mL) in the presence of toluene-p-sulfonic acid as catalyst (2 g) for 18 h at 100 °C, then cooled to room temperature and neutralized by aqueous ammonia. After concentration to dryness the residue was dissolved in the minimum of hot water and left at room temperature for crystallization. After about a week the white crystalline mass (4 g) in the bottom of the flask was filtered off. It represents 80% of the *scyllo*-inositol present in the crude product; mp 352 °C (litt [14]. 348.5–350); ^{1}H NMR (Fig. 1b) 200 MHz, δ ppm: 3.34 (s, 6H), 4.80 (s, HOD).

The *myo*-inositol derivative was separated by column chromatography on silica gel [15] and reused for further syntheses.

Acknowledgement

We thank Professor S. J. Angyal for his interest in our work.

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