The synthesis of *proto*-quercitol*

A colorless, crystalline compound, $C_6H_{12}O_5$, isolated by Braconnot[2] from the acorns of an oak tree (genus *Quercus*) and later named *quercitol*, was recognized as a new compound by Dessaignes[3]. Its structure (**1**) was established 82 years ago by Kanonnikoff[4], and its configuration (**2**) was determined 35 years ago by Posternak[5], but no synthesis has been reported.

In 1965, Angyal and co-workers[6] heated natural (−)-*vibo*-quercitol with 95% acetic acid containing a little sulfuric acid. At equilibrium, the product was shown by g.l.c. to contain acetylated *proto*-quercitol, but none was actually isolated[7].

As some authors have employed "quercitol" as a generic name (without official sanction) for the ten diastereoisomeric cyclohexanepentols, the diastereoisomer **2** (or **3**) is more explicitly termed *proto*-quercitol[8]. The *proto*-quercitol first discovered was dextrorotatory; more recently, Plouvier[9] has found the levorotatory form (**3**) in leaves of the tree *Eucalyptus populnea*. From Posternak's chemical correlations[5], it is now possible to assign the *absolute* configuration (**2**) to the dextrorotatory enantiomer. We use the systematic fractional prefix "L-(134/25)" to specify this configuration (**2**) of cyclohexanepentol.

The ten quercitols (cyclohexanepentols) constitute possibly the largest *all-known* family of diastereoisomers in organic chemistry. Although the *proto* diastereoisomer was the first to be discovered, it was the last to be synthesized.

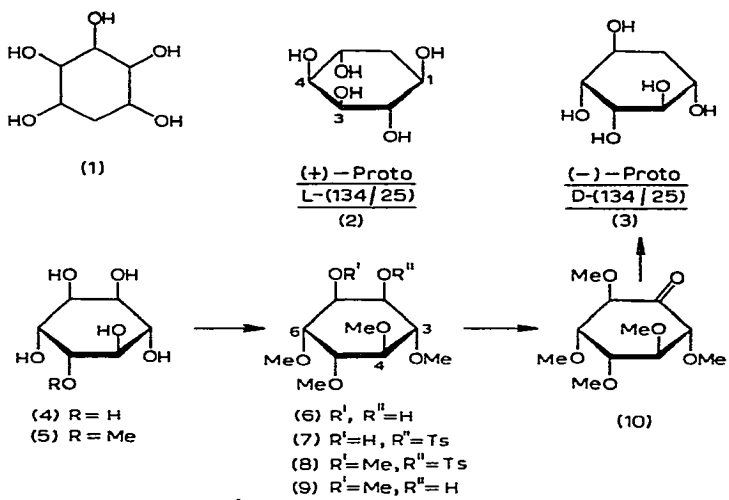
For convenience, our present synthesis started with (−)-inositol (**4**) (or quebrachitol, **5**), and thus led to (−)-*proto*-quercitol (**3**); if desired, the *identical* procedures could be applied to the well known (+)-inositol, to give (+)-*proto*-quercitol (**2**). Application of essentially identical procedures to DL-inositol would constitute a total synthesis of DL-*proto*-quercitol, because the total synthesis of DL-inositol has been reported[10]. (It is possible that some of the racemic intermediates would have different solubilities, and thus require different volumes of crystallizing solvents for best results.) DL-*proto*-Quercitol is not known to occur in Nature. Our synthesis of active *proto*-quercitol will not become "total" until DL-inositol has been resolved; Tanret[11] described the basis for a possible microbiological resolution.

First, we prepared the isopropylidene acetal of the hexol tetramethyl ether **6**, by methylating the isopropylidene acetal[8] of quebrachitol (**5**) or, somewhat less conveniently, by methylating the monoisopropylidene acetal[8] of (−)-inositol (**4**).

*Part XXXI in the series Alicyclic Carbohydrates. For part XXX, see Ref. 1.

The resulting syrup was deacetonated in the usual manner, to give the hexol tetramethyl ether* **6**, m.p. 90–92°. Selective *p*-toluenesulfonation of the equatorial hydroxyl group at C-2 gave **7**, m.p. 115–116°, which gave, on further methylation, the 2-*O*-*p*-tolylsulfonyl pentamethyl ether (**8**) as a syrup.

Treatment of **8** with sodium methoxide–ethanol gave the hexol pentamethyl ether **9** as a syrup, characterized as its monobenzoate, m.p. 88–90°. Oxidation of **9** with ruthenium dioxide–sodium periodate[12] gave (−)-*proto*-inosose pentamethyl ether (**10**), characterized as its (2,4-dinitrophenyl)hydrazone, m.p. 202–203°.



Treatment of **10** with 1,2-ethanedithiol, and reduction of the crude product with Raney nickel in boiling absolute ethanol, gave a pentol pentamethyl ether. On cleavage, this ether gave the desired (−)-*proto*-quercitol (**3**) as colorless needles, m.p. 238–239°, $[\alpha]_D^{25}$ −25.1° (*c* 1, water), (reported[9] m.p. 237°, $[\alpha]_D$ −26°). The pentabenzoate had m.p. 154–155°, $[\alpha]_D^{25}$ −62.8° (*c* 1, ethyl acetate) (reported[13] for the dextro form, m.p. 155°, $[\alpha]_D^{25}$ +61°). The i.r. spectra of the pentol and pentabenzoate were identical with those of authentic samples of the dextro form.

By recrystallizing a mixture of equal weights of the two enantiomers, we obtained DL-*proto*-quercitol, m.p. 238–239°, $[\alpha]_D$ 0° (within experimental error) (reported[9] m.p. 237°).

The diastereoisomeric configuration of (+)-*proto*-quercitol, which was first established[5] by laborious chemical correlations, has recently been confirmed[14] by p.m.r. spectroscopy at 220 MHz with a superconducting solenoid[15].

*Structures of the principal intermediates were confirmed by microanalysis, and by i.r. and p.m.r. spectroscopy; details will be reported elsewhere.

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