Accumulating evidence strongly suggests that the action of a phospholipase C on phosphoinositides in the cell membrane in response to the activation of a receptor is an integral part of an intracellular signalling pathway. Specific inhibitors of this enzyme and the site-specific kinases involved in inositide metabolism are urgently required to establish their function. An approach to the design of such inhibitors would be to replace single hydroxyl groups on myo-inositol by a fluorine atom. Such analogues would probably be incorporated into the cell by the same pathway as myo-inositol but subsequent phosphorylation at the substituted position would be blocked. Other syntheses have been published for such analogues [1, 2]. This communication reports high-yield routes to these compounds from myo-inositol and their separation as optical isomers.

The synthetic route to the meso-compound, 5-deoxy-5-fluoro-myo-inositol, is outlined in Scheme 1. The 5-position of compound 1, available in good yield by the method of Garegg & Lindberg [3], was inverted to give the neo-inositol derivative by nucleophilic displacement of a toluene-sulphonate group so that fluorination with diethylamino-
sulphur trifluoride would leave it with the required myo-configuration [4]. The final product was obtained in 73% yield from compound 1.

Initial trials at synthesizing the 1(3)-substituted compounds from cyclohexylidene-protected inositol derivatives were unsuccessful because attempts at inverting the 1-position by nucleophilic displacement gave the elimination product. This problem was avoided by the strategy shown in Scheme 2. Compound 6, available in three steps by the method of Gigg & Warren [5], was tosylated exclusively at the 1-position. This compound was then fluorinated to give a scyllo-inositol derivative in 85% yield. To recover the myo-configuration, the tolenesulphonate group was displaced by the caesium salt of optically active camphanic acid in 90% yield. In addition, this step allowed the separation of the two resulting diastereomers by column chromatography. They were then deprotected quantitatively by base hydrolysis of the camphanate followed by hydrogenolysis of the benzyl protecting groups. The advantages of this route are that the inversion necessary to obtain the required configuration and the resolution of the enantiomers can be combined into a single step, and that the reactions involved in the pathway occur in high yield from a readily available starting material.
Brown-fat pyruvate dehydrogenase activities during the fed-to-starved transition

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Insulin-deficiency induced by anti-insulin serum elicits a dramatic decline in the activity of the pyruvate dehydrogenase complex (PDH) in brown fat [1]. In the present study, we have defined the time course of PDH inactivation in brown fat after insulin deficiency induced by food withdrawal, and investigated whether the duration of starvation influences the initial response of brown-fat active PDH (PDHa) to insulin replacement. We have also investigated the relationship between PDHa activity and the lipogenic rate during the fed-to-starved transition and after insulin replacement.

Adult female rats were fed ad libitum on standard diet (52% carbohydrate) before food withdrawal at 08:30 h. Insulin (2 units) was injected subcutaneously and rats were sampled after 0.5 h [2]. PDHa and citrate synthase activities were measured as described by Caterson et al. [3]. PDHa activities are expressed relative to citrate synthase activities to correct for variable efficiency of mitochondrial extraction. Lipogenic rates were measured using H20 [4].

A decline in PDHa activity in brown fat occurred within 2–3 h of food withdrawal. After 4 h, PDHa activity was 42 ± 7% of the fed value (10.7 ± 1.0 minunits/unit of citrate synthase, n = 7), and after 6 h it was only approx. 25% of the fed value (Fig. 1). Inactivation was complete after 48 h starvation (Fig. 1).

Insulin administration dramatically increased brown-fat PDHa activity in the fed state (Fig. 1). PDHa activities at 0.5 h after insulin treatment were significantly lower in rats starved for 6 h than in fed rats, but the absolute increment in PDHa activity induced by insulin was approximately similar (Fig. 1). Brown-fat PDH was refractory to complete reactivation by insulin within a 30 min period of exposure if the starvation period was extended to 48 h (Fig. 1). However, after 1 h of exposure PDHa activity exceeded that in the fed state (results not shown).

Glucose is a major precursor for brown-fat lipogenesis (reviewed by McCormack, [5]). In the fed state the rate of lipogenesis, expressed as acetyl-group equivalents, approximated to PDHa activity (see the legend to Fig. 1). Rates of lipogenesis after starvation for 6 h or 48 h were 36% or 39% of those found in the fed state (Fig. 1). In both fed and 6 h-starved rats, relative rates of lipogenesis bore a close relationship to the relative activities of PDHa (Fig. 1). Furthermore, in both states (fed and 6 h-starved), the increases in PDHa activities elicited by insulin were closely paralleled by increases in rates of lipogenesis. The results indicate that PDH may exert a strategic regulatory influence on lipogenesis or that PDHa activities and rates of lipogenesis are co-variate.

PDHa activity in brown fat after 48 h-starvation was lower than that required to sustain the observed rate of lipogenesis.

Abbreviations used: PDH, pyruvate dehydrogenase complex; PDHa, active form of the pyruvate dehydrogenase complex.

Fig. 1. PDHa activity and rate of lipogenesis

PDHa activities (■, measured at 30°C) and rates of lipogenesis (■, measured in vivo using H20) after 6 h or 48 h starvation are expressed as percentages of those found in rats fed ad libitum (values of 10.7 ± 1.0 minunit/unit of citrate synthase (40.2 acetyl-group equivalents/h per g) and 114.0 ± 11.6 µ-atoms of H/h per g wet wt. (69.0 acetyl-group equivalents/h per g)]. PDHa activities were measured at 0.5 h after the injection of insulin (2 units) or an equivalent volume of 0.9% (w/v) NaCl. Rates of lipogenesis were measured over the first hour after the injection of insulin or NaCl. Results are means for six to ten rats. Error bars have been omitted for clarity. Statistically significant effects of starvation: tP < 0.05; t+tP < 0.01; t+t+tP < 0.001. Statistically significant effects of insulin: ***P < 0.001.

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