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PREPARATION OF A CYCLOHEXANONE INTERMEDIATE FOR SYNTHESIS OF THROMBOXANE ANTAGONISTS

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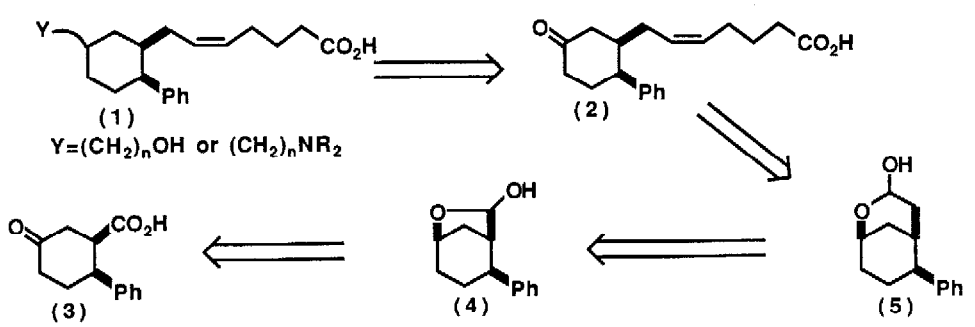
Summary : An efficient route to cyclohexanone (2) is reported, providing multigram quantities of (2) in 35% overall yield from ketoacid (3).

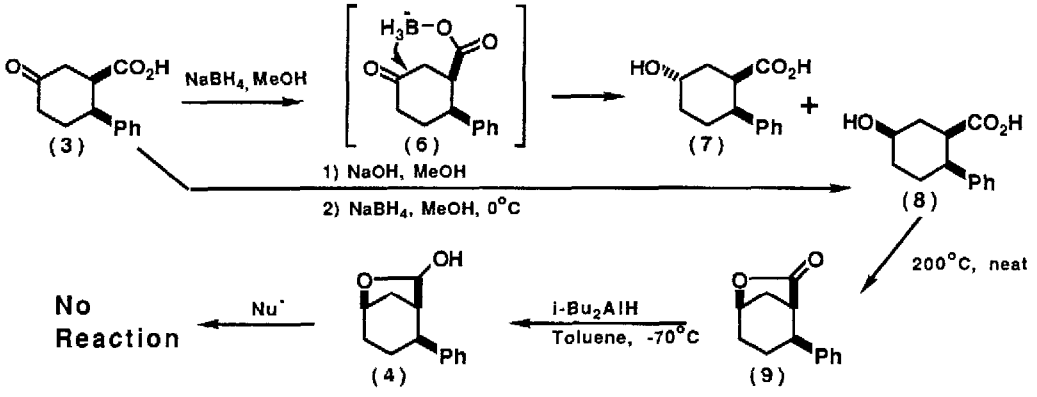
As part of a program of research into the development of selective thromboxane receptor antagonists, we required a high throughput route to cyclohexanone (2), in order to prepare a series of analogs of general structure (1).



Our starting point was the cyclohexanonecarboxylic acid (3), reported by Ziegler[1]. The strategy was to convert (3) into bicyclic lactol (4), homologate this to lactol (5), and introduce the alkenoate side chain using standard Wittig methodology[2].

The sequence commenced with reduction of the ketone group of ketoacid (3). Treatment of (3) with sodium borohydride gave a mixture of diastereomeric alcohols (7) and (8)[3], with the unwanted isomer (7) predominating in a ratio of about 3:2. Preferential attack on the more substituted face of (3) may be explained by intramolecular delivery of hydride from an intermediate such as (6).

It was reasoned that formation of a species such as (6), and hence formation of alcohol (7), would be precluded if acid (3) were converted to its carboxylate anion prior to reduction. In practice, pretreatment of (3) with sodium hydroxide, followed by addition of sodium borohydride, now resulted in exclusive attack from the less substituted face, to give (in 77% yield) all-*cis* alcohol (8) as the only observed product. Thermal dehydration afforded a 94% yield of lactone (9), which underwent reduction to lactol (4) upon treatment with DIBAH.

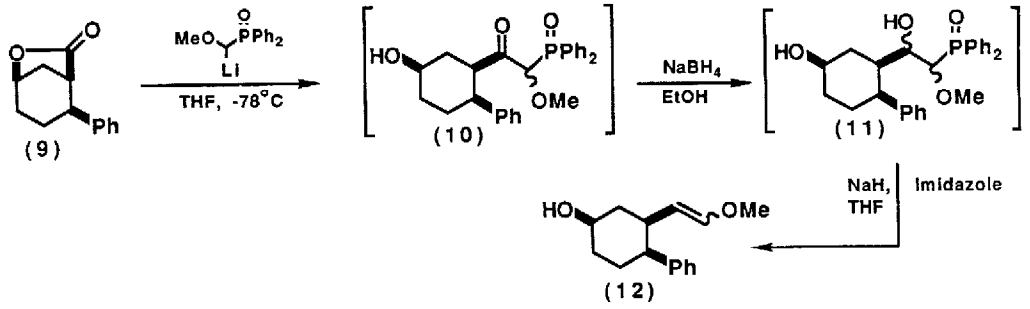


The plan was now to effect homologation of (4) using one of several standard methods[4-6]. This was thwarted, however: various reagents, such as methoxymethyltrimethylsilane[4], methoxymethylenetriphenylphosphorane[5], and methoxymethyldiphenylphosphine oxide[6], failed under a variety of conditions to undergo addition to lactol (4).

Possible reasons for this failure include: i) unfavourable equilibrium between (4) and the hydroxyaldehyde tautomer required for reaction (the reluctance of five-membered-ring lactols to undergo ring-opening has been documented[7], although Wittig-type reagents are reportedly efficient at trapping out the ring-opened tautomer[8]); and ii) ready enolisation of any aldehyde which does form.

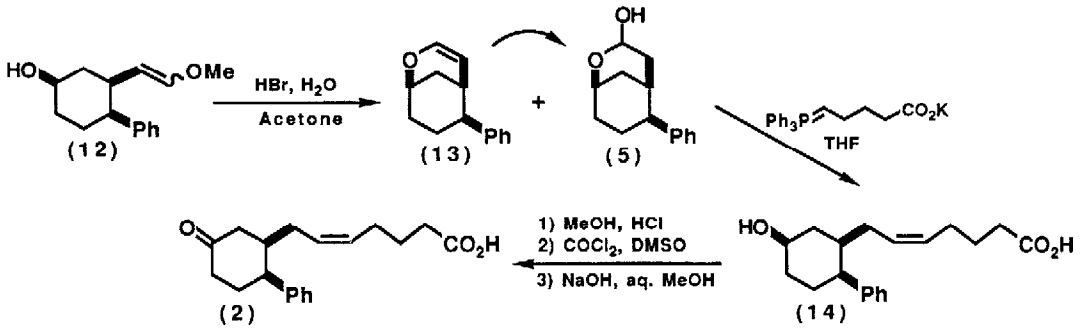
It was felt that both of these problems could be circumvented if the homologating agent could be persuaded to undergo addition to lactone (9), rather than to lactol (4) (since tautomerisation would no longer be an issue, and enolisation could not interfere). It is known that phosphorus-stabilised anions can react with lactone carbonyl groups[9], and lactone (9) proved no exception, as demonstrated below.

Thus, addition of the anion of methoxymethyldiphenylphosphine oxide to (9) gave a high yield of a poorly characterised adduct, which was presumed to comprise (10) and its hemiacetal tautomer, both as diastereomeric mixtures.



This was reduced cleanly with sodium borohydride[9] to a second poorly defined intermediate (a mixture of isomers of (11)), which underwent smooth elimination to enol ether (12) (as a 70:30 mixture of E:Z isomers), upon treatment with sodium hydride[9]. Overall yield for the conversion of (9) to (12) was 80%.

Hydrolysis of (12) in aqueous acetone afforded, surprisingly, a mixture of the desired lactol (5), together with an almost equal amount of bicyclic enol ether (13).



That this represented an equilibrium mixture was demonstrated by resubmitting either product to the hydrolysis conditions, whereupon the same mixture was obtained. The two compounds were readily separated, however, and the enol ether re-equilibrated to give, after a single recycle, a 75% yield of lactol (5). The highly facile dehydration of (5) (which occurs simply upon standing) precluded its satisfactory characterisation. Its identity was confirmed by the success of the subsequent Wittig reaction[2], which afforded a 92% yield of hydroxy-acid (14).

Conversion of (14) through to the target ketoacid (2) could be achieved by direct oxidation with PCC[10], although yields were modest and irreproducible. The transformation could be carried out in much more reliable fashion via: i) esterification; ii) Swern oxidation[11]; and iii) saponification. Overall yields of 85% could be realised using this three-step sequence.

Ketoacid (2) can be prepared readily on a 20gm scale by the route outlined above, and in 35% overall yield from starting ketoacid (3). Preparation of potential thromboxane antagonists from this key compound is now underway.

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