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REGIOSELECTIVE EPOXIDE-CARBONYL REARRANGEMENTS: A RING ENLARGEMENT OF CYCLOBUTANONES TO CYCLOPENTANONES.

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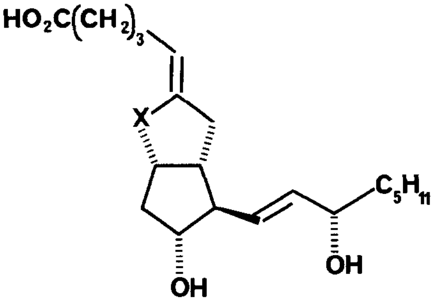
A versatile, direct approach to derivatised bicyclo(3,3,0)octanones, involving a regiocontrolled epoxide-carbonyl rearrangement, is described.

Recently much attention has been focussed on synthetic strategies that lead to the bicyclo(3,3,0)octane system, a structural unit shared by a variety of sesquiterpenes.[1,2] Moreover, many carbocyclic analogues of PGI_2 (prostacyclin, 1) such as carbacyclin (6a-carbaprostacyclin, 2), also possess this skeletal framework.

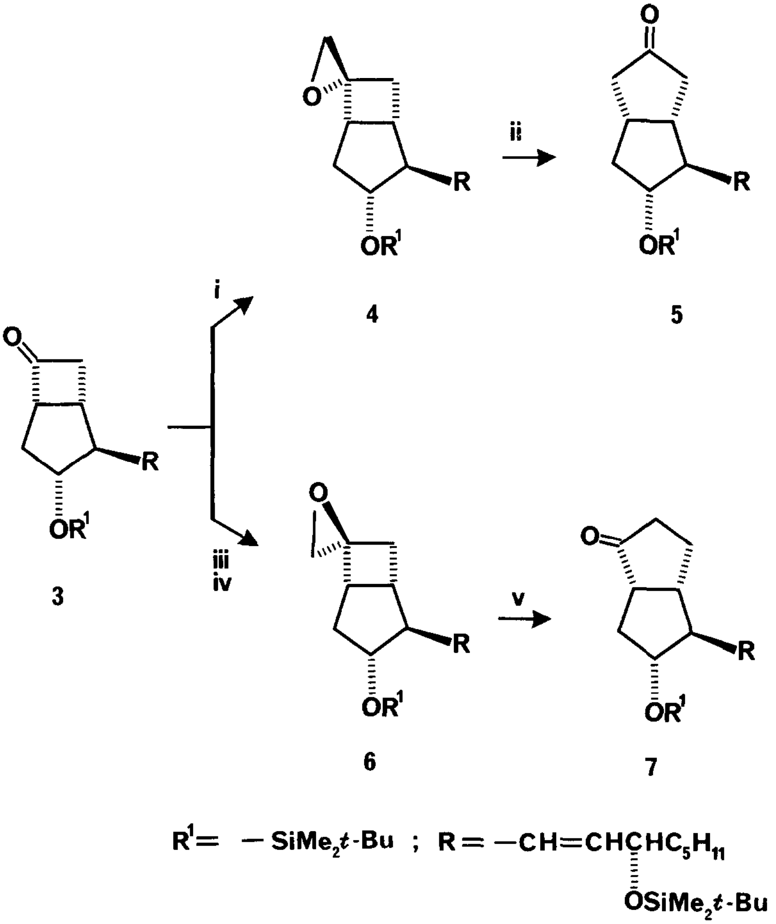


1, X = O
2, $X = CH_2$

Scheme 1

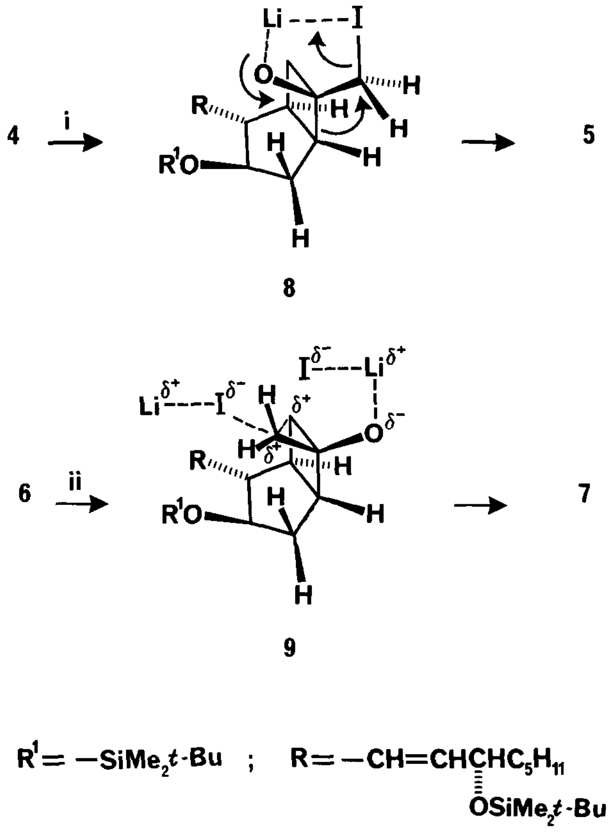
We report herein a regiocontrolled synthesis of the two important synthons 5 and 7, both of which have been extensively used in the synthesis of prostacyclin analogues.[3,4] However, since the general conversion of cyclobutanones to cyclopentanones is also an important feature of many natural product syntheses,[1-10] perhaps the most notable aspect of our work is the intriguing selectivity of bond migration observed during the rearrangements of the α-epoxide 4, and the ß-epoxide 6, to the isomeric ketones 5 and 7 respectively.

The racemic, protected dihydroxybicyclo(3,2,0)heptanone derivative 3, was prepared using known literature procedures.[11,12] Thereafter 3 was selectively converted to the α-epoxide 4 in 90% yield, using the method of Corey and Chaykovsky[13] (trimethylsulphonium iodide, sodium dimsylate, dimethylsulphoxide-tetrahydrofuran (1:1), 0°C[#]. The subsequent epoxide-carbonyl rearrangement of 4 proceeded in a regioselective manner (lithium iodide, tetrahydrofuran, 20°C, 4 hours) affording the ketone 5 in 68% yield and its isomer 7 in 10% yield, after chromatography. The corresponding ß-epoxide 6 was subsequently prepared in 70% overall yield, from the bicycloheptanone 3, after initial conversion to the analogous methylene derivative using the method of Lombardo,[14] followed by a regiospecific epoxidation (m-chloroperbenzoic acid, CH_2Cl_2, 0°C). In direct contrast to the previous cleavage of the α-epoxide 4, the ß-epoxide 6 underwent a slow, regioselective rearrangement (lithium iodide, tetrahydrofuran, 20°C, 60 hours) affording the ketone 7 in 71% yield and less than 10% of ketone 5.



Scheme 2. i, Me_3SI, sodium dimsylate, DMSO-THF (1:1), 0°C; ii, LiI, THF, 20°C, 4 hours; iii, '$BrZnCH_2TiCl_3$', CH_2Cl_2, 0°C, (ref. 14); iv, m-CPBA, CH_2Cl_2, 0°C; v, LiI, THF, 20°C, 60 hours.

In a complementary approach, the importance of a coordinated lithium counterion upon the mode of bond migration was further demonstrated during the diazomethane-effected ring expansion of ketone 3.[15,16] Thus treatment of 3 with diazomethane in methanol-diethylether at 20°C afforded approximately a 50:50 mixture of ketones 5 and 7, whereas with diazomethane, in diethylether containing lithium perchlorate at 20°C, a 1:4 mixture of 5 and 7 respectively was obtained. These results appear to be consistent with the empirical results obtained on other similar systems.[2a,7,12,15]



Scheme 3. i, LiI, THF, 20°C, 4 hours; ii, LiI, THF, 20°C, 60 hours.

We suggest that the mechanistic mode of these epoxide-carbonyl rearrangements is largely dictated by the considerable steric interactions and torsional strain inherent in the bicyclo[3,2,0]heptane system. Thus the α-epoxide 4, being readily susceptible to nucleophilic attack, is thought to form a 5 membered anti-periplanar transition state 8, which then undergoes a synchronous rearrangement to ketone 5. This pathway, however, owing to steric crowding at the α-face, is not available to the β-epoxide 6, which is thought to form ketone 7 via the corner protonated cyclopropane transition state 9.

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14. L. Lombardo, Tetrahedron Lett., 1982, 23, 4293. In a modification of this procedure we found that more reproducible results were obtained when the initial reaction between zinc and dibromomethane was allowed to proceed at 20°C for 15 minutes prior to cooling to -40°C and subsequent reaction with titanium tetrachloride.

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\# *Satisfactory spectroscopic and elemental data were obtained for all new compounds.*

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