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Synthesis of Chiral Cyclobutane Derivatives by Tetrahydropyran Ring-Opening[1]

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Key Words: glycals, tetrahydropyran ring-opening, chiral cyclobutanones.

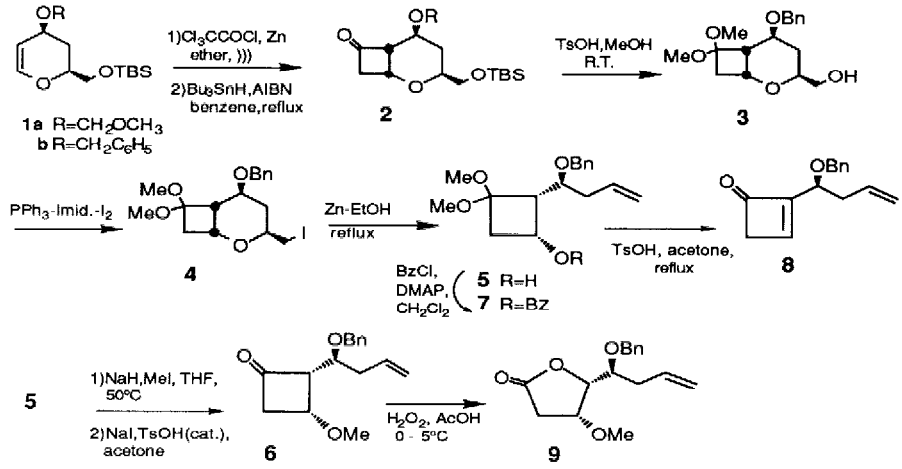
***Abstract**: Optically active cyclobutane derivatives were synthesized from chiral 2-oxabicyclo[4.2.0]octanone 2 by zinc- induced tetrahydropyran ring-opening.*

Cyclobutane derivatives have emerged as versatile intermediates for the preparation of natural as well as unnatural products[2]. During the past three years, the chemistry of this class of compounds has enjoyed even more interest due to their interesting biological properties. For instance, cyclobutane nucleosides exhibit potent antiviral activity and act as anticancer agents[3,4].

Obviously, access to optically active cyclobutane derivatives would greatly enhance their usefulness in the enantioselective synthesis of natural products. To this end, some approaches have been reported[2a] involving optical resolutions and asymmetric synthesis using chiral auxiliairies[5,6] or chiral catalyst[7]. Hitherto, only few syntheses from chiral building blocks have been mentioned in the litterature[2a].

We have recently reported the synthesis of optically active 2-oxabicyclo[4.2.0]octanone **2** by cycloaddition of 1,1-dichloroketene to glycals **1** followed by dehalogenation. These products have been found to be valuable intermediates for the anomeric alkylation and vicinal bifunctionalization of starting glycals via the regioselective cleavage of the cyclobutane ring[1]. We wish to report here that the same products readily suffer cleavage of the tetrahydropyran ring leading to cyclobutane derivatives.

Treatment of **2** with p-toluenesulfonic acid (1.1 equiv) in methanol at room temperature induced deprotection of the primary hydroxy group and conversion of the ketone to dimethyl acetal affording **3** in 87% yield. Iodination of this alcohol was smoothly effected with the triphenylphosphine/imidazole/iodine reagent to give **4** in 93% yield. The reductive tetrahydropyran ring-opening was readily achieved by treatment **4** with zinc in refluxing ethanol to give cyclobutanol **5**[8] in 98% yield. This alcohol can be transformed into various cyclobutane derivatives using a standard series of reactions. Thus, protection of hydroxy group in **5** as methyl ether (NaH, MeI) followed by hydrolysis of the dimethyl acetal furnished ketone **6**[8] in 90% overall yield. It should be noted that acid hydrolysis of the acetal directly from alcohol **5** or via benzoate **7** led to the chiral cyclobutenone **8** in high yields (Scheme).



The application of these cyclobutane derivatives as intermediates in organic synthesis is illustrated by the preparation of chiral γ-lactones. Baeyer-Villiger oxidation (hydrogen peroxide in aqueous acetic acid at 0-5°C) of the ketone **6** occured chemo- and regioselectively with retention of configuration affording pure lactone **9**[8] in 90% yield.

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8. All new compouds were fully characterized by their $[\alpha]_D$, IR, ^1H and ^{13}C NMR. **5**: $[\alpha]_D$ = + 28 (c = 2.59, $CHCl_3$) IR(CCl_4) 3569, 3067, 1639, 1453, 1255, 1178 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$); δ 2.05 - 2.18 (m, 2H), 2.27-2.45 (m, 2H), 2.53-2.70 (m,2H), 3.20 (s, 3H), 3.27 (s,3H), 3.87 (dt J=9.5, 5.0 Hz,1H), 4.15 - 4.27 (m, 1H), 4.56 (d, J=11.2 Hz, 1H), 4.65 (d, J=11.2 Hz, 1H), 5.06 - 5.20 (m, 2H), 5.85 - 6.01 (m, 1H), 7.23 - 7.37 (m, 5H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 36.1, 40.7, 48.3, 50.3, 62.9, 71.5, 73.8, 102.9, 117.1, 127.3, 127.8, 128.2, 134.9, 138.7. **6**: $[\alpha]_D$= - 60 (c = 2.94,); IR 3067, 1789, 1640, 1547, 1210, 1111 cm^{-1}; ^1H NMR δ 2.37 - 2.57 (m, 2H), 3.0-3.15 (m, 2H), 3.31 (s, 3H), 3.39 - 3.50 (m, 1H), 3.87 (q, J=5.8Hz, 1H), 4.08 - 4.25 (m, 1H), 4.53 (d, J=11.2Hz, 1H), 4.64 (d, J=11.2Hz, 1H), 5.00 - 5.20 (m, 2H), 5.71 - 5.91 (m, 1H), 7.17 - 7.36 (m, 5H); ^{13}C NMR δ 37.8, 52.7, 56.9, 66.7 , 68.1, 71.8, 74.6, 117.7, 127.3, 127.9, 128.1, 134.4, 138.6, 206.0. **9**: $[\alpha]_D$= + 12 (c = 2.15); IR 3067, 1796, 1640, 1555cm^{-1}; ^1H NMR δ 2.23 - 2.49 (m, 2H), 2.54 (dd, J=14.2, 2.4 Hz, 1H), 2.70 (dd, J=14.2, 3.2 Hz, 1H), 3.29 (s, 3H), 3.87 (m, 1H), 4.03 - 4.12 (m, 1H), 4.43 (dd, J=6.7, 4.8Hz, 1H), 4.59 (d, J=11.3Hz,1H), 4.72 (d, J=11.3Hz, 1H), 5.07 - 5.17 (m, 2H), 5.79 - 6.00 (m, 1H), 7.20 - 7.36 (m, 5H); ^{13}C NMR δ 34.5, 35.0, 56.7, 72.8, 76.5, 84.8, 117.6, 127.4, 127.6, 128.1, 133.8, 138.3, 174.6.

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