Stereoselective Favorskii Rearrangement of Carvone Chlorohydrin; Expedient Synthesis of (+)-Dihydronepetalactone and (+)-Iridomyrmecin

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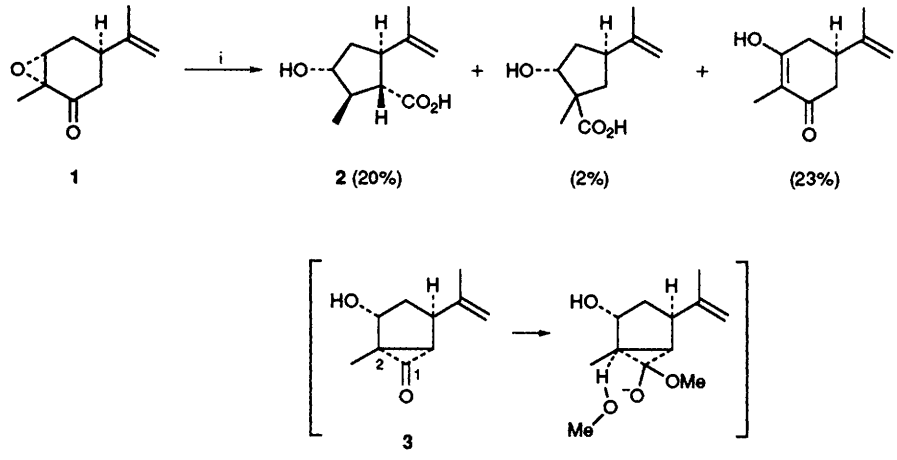
(+)-Dihydronepetalactone and (+)-iridomyrmecin were synthesized from the stereoselective Favorskii rearrangement product of (+)-carvone chlorohydrin.

Functionalized cyclopentanecarboxylates are obtained from the Favorskii rearrangement of cyclohexanone derivatives, *e.g.*, Favorskii rearrangement of the monoepoxide **1** of (−)-carvone afforded a highly functionalized cyclopentanecarboxylic acid **2** albeit in low yield[1] (Scheme 1).

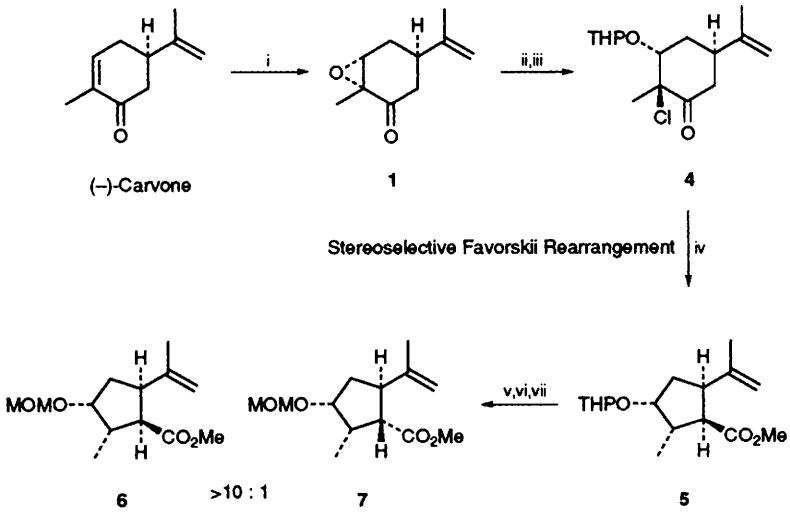
The stereochemical array in **2** requires cyclopropanone derivative **3** as an intermediate (presumably formed by the S_N2 type displacement of the epoxide moiety) in which the selective cleavage of the bond between C-1 and C-2 is coupled with the stereoselective protonation at C-2 resulting in retention of the stereochemistry. We prepared the chlorohydrin derivative of (−)-carvone to examine Favorskii rearrangement. The Favorskii rearrangement of the chlorohydrin **4** is very efficient and provides a valuable cyclopentanecarboxylate derivative **5**, and its enantiomer **8** is converted into cat-attracting iridolactones,[2] (+)-dihydronepetalactone **11**[3] and (+)-iridomyrmecin **14**.[4]

The monoepoxide **1** of (−)-carvone was treated with chlorotrimethylsilane in acetonitrile containing Me_2SO[5] and the resulting chlorohydrin was converted into the corresponding THP (tetrahydropyranyl) ether **4**. When **4** was treated with NaOMe in MeOH at room temp., a facile rearrangement occurred and a high yield of the cyclopentanecarboxylate was isolated. Conversion to the corresponding MOM (methoxymethyl) ether **6** confirmed that the rearrangement was stereoselective affording the thermodynamically less stable cyclopentanecarboxylate **5**† (Scheme 2).

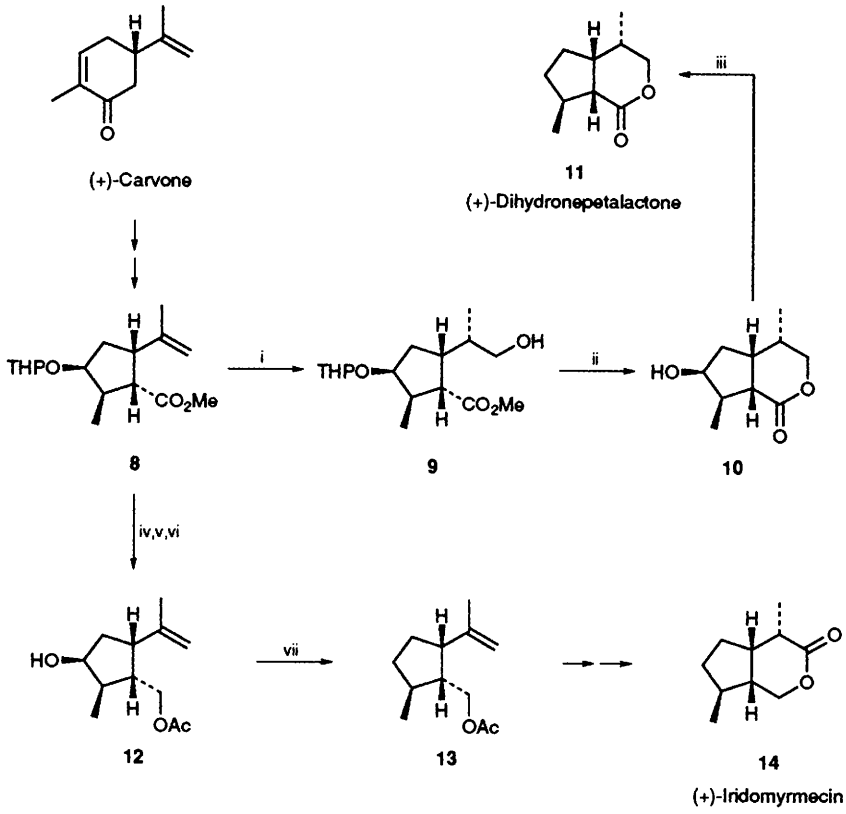
For the synthesis of naturally occurring iridolactones, (+)-carvone was converted into **8** using identical procedures. Stereoselective hydroboration with disiamylborane and oxidation led to the primary alcohol **9**, and lactonization under basic conditions and acid treatment afforded the hydroxylactone **10**. Barton type deoxygenation of **10** yielded (+)-dihydronepetalactone **11**‡ (Scheme 3).



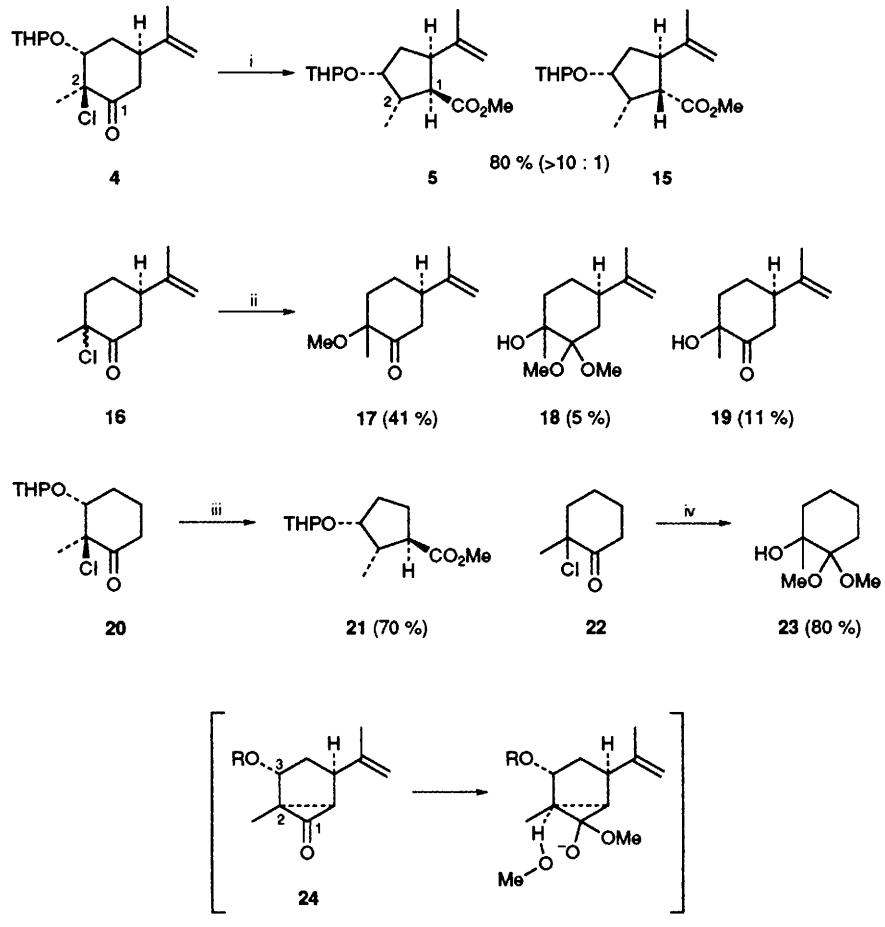
Scheme 1 *Reagents and conditions*: i, EtONa, EtOH, 80 °C, 2 h



Scheme 2 *Reagents and conditions*: i, H_2O_2, 2 mol dm^{-3} NaOH, MeOH, room temp., 1 h, 90%; ii, TMSCl (1.5 equiv.), Me_2SO (1.5 equiv.), MeCN, room temp., 10 min, 85%; iii, DHP, cat. *p*-TsOH, CH_2Cl_2, room temp., 1 h, 95%; iv, MeONa (1.5 equiv.), MeOH, room temp., 10 min, 80%; v, cat. *p*-TsOH, MeOH, reflux, 20 min, 90%; vi, MOMCl (1.5 equiv.), DIPEA (1.5 equiv.), cat. DMAP, CH_2Cl_2, room temp., 6 h, 95%; vii, chromatography (Ts = tosyl, TMS = trimethylsilyl, DHP = dihydropyran, DIPEA = diisopropylethylamine, DMAP = dimethylaminopyridine)



Scheme 3 *Reagents and conditions*: i, Disiamylborane, THF, 0 °C, H_2O_2, aq. NaOH, 85%; ii, KOH, aq. MeOH, reflux, HCl (pH 1), 81%; iii, $NaH/CS_2/MeI/Bu_3SnH$, cat. AIBN, Benzene, reflux 75%; iv, LAH, diethyl ether; v, Ac_2O, cat. DMAP, pyridine; vi, cat. *p*-TsOH, MeOH, room temp. 75%; vii, $NaH/CS_2/MeI/Bu_3SnH$, cat. AIBN, Benzene, reflux, 75%.



Scheme 4 *Reagents and conditions*: MeONa (1.5 equiv.), MeOH, room temp., i, 10 min; ii, 10 min; iii, 1 h; iv, 10 min.

Alternatively, the cyclopentanecarboxylate **8** was transformed into the acetate **12** *via* LAH reduction, acetylation, and acid deprotection. Routine deoxygenation of **12** led to the acetate **13**, a known intermediate in the synthesis of (+)-iridomyrmecin **14**.[6]

The efficient Favorskii rearrangement of the chlorohydrin derivative **4** which resulted in the stereoselective formation of **5** was remarkable, and further examples were studied to provide better understanding of various factors influencing these reactions. The chloroketone **16** did not yield any Favorskii rearrangement product under similar conditions. The chlorohydrin derivative **20** rearranged more slowly, but comparable yield of cyclopentanecarboxylate **21** was isolated. The simplest chloroketone **22** did not yield the Favorskii rearrangement product[7] (Scheme 4).

From the results obtained it is clear that 3-oxy substituents play a critical role in the Favorskii rearrangement of 2-chlorocyclohexanones. In the rearrangement of **4** to **5**, two new secondary stereo centres are generated at C-1 and C-2. The configuration at C-1 of **5** is determined by the configuration at C-2 of **4** *via* S_N2 type displacement of chloride in forming the cyclopropanone derivative **24**. The presence of the 3-OTHP group in **24** (and 3-OH in **3**) induces selective cleavage of the adjacent bond between C-1 and C-2.[8,9] Remarkably, protonation at C-2 of **5** occurs with the complete retention of stereochemistry.

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Footnotes

† It is important to maintain low reaction temperature for high yield of **5**. Reaction of **4** with 1.5 equiv. NaOMe in refluxing MeOH for 1 h and conversion into the MOM ether led to the isolation of **6** and **7** in 1:2 ratio (85% yield).

‡ ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (dd, 1H, *J* 9.9, 11.1 Hz), 4.03 (ddd, 1 H, *J* 1.5, 4.2, 11.1 Hz), 2.52 (m, 1H), 2.43 (dd, 1H, *J* 9.0, 10.8 Hz), 2.24 (m, 1H), 2.06–1.89 (m, 2H), 1.81–1.71 (m, 2H), 1.50–1.22 (m, 2H), 1.21 (d, 3H, *J* 6.3 Hz), 0.90 (d, 3H, *J* 6.9 Hz); ^{13}C NMR (20.2 MHz, $CDCl_3$) δ 12.87, 19.12, 26.17, 30.75, 34.82, 40.27, 41.25, 50.33, 69.75, 174.03; IR (cm^{-1}) 2960, 1724; MS (EI) 168 (M^+, 8), 153(32), 139(4), 126(26), 113(45), 95(30), 81(100), 67(85); $[\alpha]_D^{23}$ +77.9 (c 0.47, CCl_4).

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