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 yield¹ (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 11³ and (+)-iridomyrmecin 14.⁴

The monoepoxide 1 of (-)-carvone was treated with chlorotrimethylsilane in acetonitrile containing Me₂SO⁵ 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.), Me₂SO (1.5 equiv.), MeCN, room temp., 10 min, 85%; iii, DHP, cat. *p*-TsOH, CH₂Cl₂, 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, CH₂Cl₂, room temp., 6 h, 95%; vii, chromatography (Ts = tosyl, TMS = trimethylsilyl, DHP = dihydropyran, DIPEA = diisopropylethylamine, DMAP = dimethylaminopyridine)

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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/CS₂/Mel/Bu₃SnH, cat. AIBN, Benzene, reflux 75%; iv, LAH, diethyl ether; v, Ac₂O, cat. DMAP, pyridine; vi, cat. *p*-TsOH, MeOH, room temp. 75%; vii, NaH/CS₂/Mel/Bu₃SnH, 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.

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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 product⁷ (Scheme 4).

From the results obtained it is clear that 3-oxy substituents play a critical role in the Favorskii rearrangement of 2chlorocyclohexanones. 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).

[‡] ¹H NMR (300 MHz, CDCl₃) & 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); ¹³C NMR (20.2

MHz, CDCl₃) 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); [α]²³_D +77.9 (c 0.47, CCl₄).

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