

## Baeyer–Villiger Oxidation of Bicycloheptanone to Cyclopentapyranone: a Novel Synthesis of Iridomyrmecin, Isoiridomyrmecin, and Boschnialactone

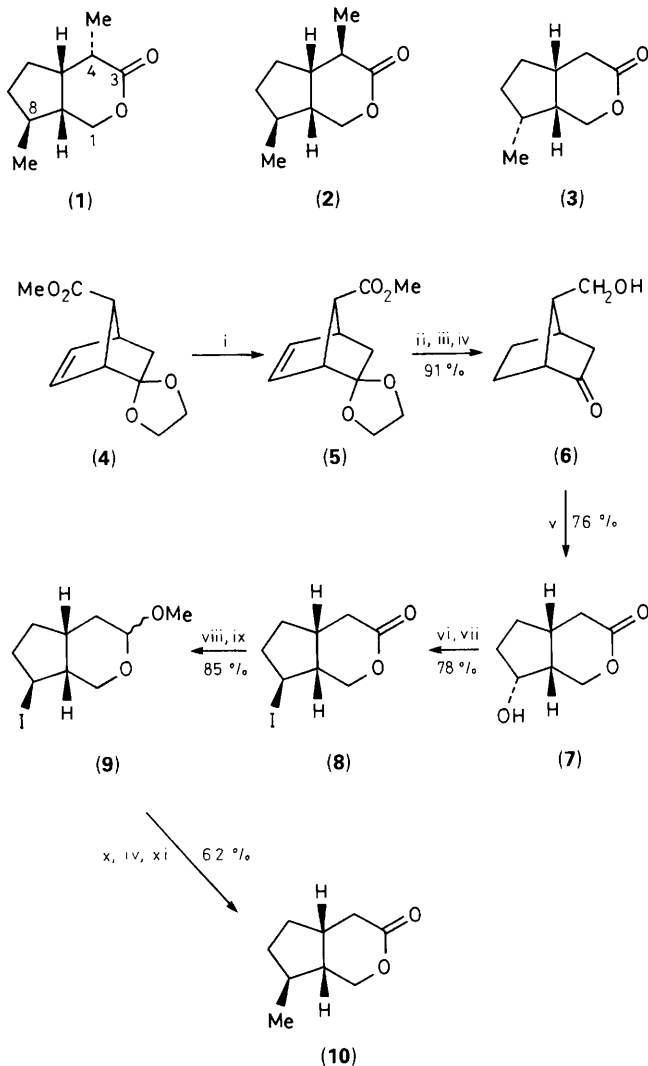
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Stereocontrolled syntheses of iridomyrmecin, isoiridomyrmecin, and boschnialactone are accomplished through a Baeyer–Villiger oxidation and either a cuprate coupling reaction or catalytic hydrogenation.

Insect repellents, iridomyrmecin (**1**), isoiridomyrmecin (**2**), and boschnialactone (**3**) are logical synthetic targets owing to their simple and well defined structures.<sup>1</sup> The cyclopentapyranone skeleton and the three contiguous non-epimerizable stereogenic centres are the focal point of the synthetic

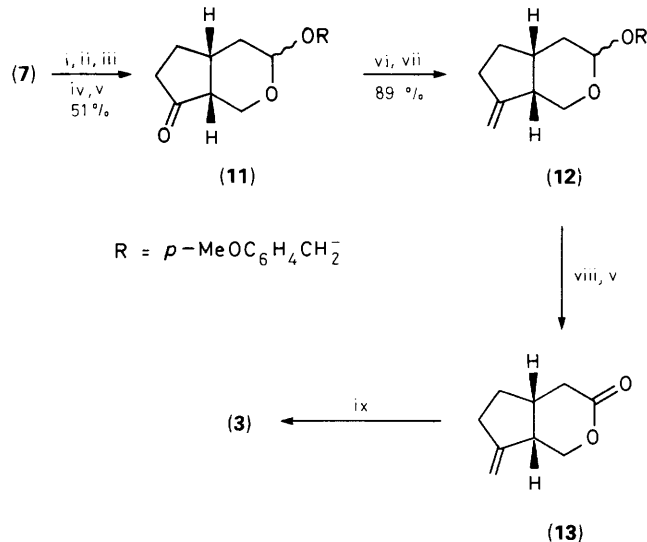
approaches.<sup>2</sup> Structurally rigid bicyclo[2.2.1]heptanone is a pertinent precursor for this purpose. With a *C*-7-hydroxymethyl group *syn* to the keto group, a *cis* ring juncture of the cyclopentapyranone ring system could be obtained *via* a Baeyer–Villiger reaction.



**Scheme 1.** Reagents and conditions: i,  $\text{Pr}_2\text{NLi}$ , THF, 0 °C, 30 min, then AcOH; ii, 10% Pd/C,  $\text{H}_2$ , EtOAc; iii,  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ ; iv, toluene-*p*-sulphonic acid (*p*-TsOH), wet acetone; v, *m*-chloroperoxybenzoic acid,  $\text{NaHCO}_3$ ,  $\text{CH}_2\text{Cl}_2$ ; vi,  $\text{PhSO}_2\text{Cl}$ , pyridine; vii, NaI, acetone; viii, di-isobutylaluminium hydride (Dibal-H), THF; ix, pyridinium toluene-*p*-sulphonate (PPTS), MeOH; x, 2 equiv. MeLi, copper(I) bromide-dimethyl sulphide,  $\text{Et}_2\text{O}$ , -78 °C to room temp., overnight; xi, PDC,  $\text{CH}_2\text{Cl}_2$ .

Acetal ester (4) (6 steps from 2,5-norbornadiene)<sup>3</sup> (Scheme 1) was epimerized to the isomeric acetal ester (5), having the methoxycarbonyl group *syn* to the acetal group, by treatment with lithium di-isopropylamide in tetrahydrofuran (THF) followed by a kinetic protonation.<sup>†</sup> Catalytic hydrogenation, followed by a lithium aluminium hydride reduction and acetal hydrolysis, provided keto alcohol (6) in 91% yield. Baeyer-Villiger rearrangement<sup>4</sup> of (6) was performed in dichloromethane, using *m*-chloroperoxybenzoic acid as an oxidant and sodium hydrogen carbonate as a base. The reaction does not stop at the Baeyer-Villiger product but further transformation *via* an intramolecular transesterifica-

<sup>†</sup> Kinetic protonation provided in quantitative yield about 3 : 1 to 5 : 1 ratio of (5) to (4). The desired (5) could be obtained by fractional crystallization in pentane at -20 °C. One operation could provide up to 40–45% of (5). The mixture of (4) and (5) was recycled. Recently we have found that the corresponding *t*-butyl ester gives greater efficiency in the fractional crystallization step.



**Scheme 2.** Reagents and conditions: i,  $\text{Bu}^t\text{SiMe}_2\text{Cl}$ , imidazole, 4-dimethylaminopyridine,  $\text{CH}_2\text{Cl}_2$ ; ii, Dibal-H, THF; iii, 4-methoxybenzyl alcohol, *p*-TsOH,  $\text{CH}_2\text{Cl}_2$ ; iv,  $\text{Bu}_4\text{NF}$ , THF; v, PDC,  $\text{CH}_2\text{Cl}_2$ ; vi,  $\text{Me}_3\text{SiCH}_2\text{Cl}$ , Mg,  $\text{Et}_2\text{O}$ , then (11); vii, KH, THF; viii, DDQ,  $\text{H}_2\text{O}$ ,  $\text{CH}_2\text{Cl}_2$ ; ix,  $(\text{PPh}_3)_3\text{RhCl}$ ,  $\text{H}_2$ , benzene.

tion occurs giving the desired cyclopentapyranone (7)<sup>‡</sup> in 76% yield. The <sup>1</sup>H NMR spectrum of the corresponding acetate shows only one proton shift downfield [ $\delta$  5.27 (1H, q, *J* 6.3 Hz)] suggesting structure (7). Introduction of a C-8  $\beta$ -methyl group was found to be a troublesome. However, the problem was solved *via* a methyl cuprate coupling reaction and is described as follows.

Alcohol (7) was treated with benzenesulphonyl chloride in pyridine, and the resulting benzenesulphonate was then treated with sodium iodide in acetone to give iodolactone (8) in 78% yield. The lactone functionality was transformed to an acetal *via* a di-isobutylaluminium hydride reduction and methanolysis gave iodide (9) in 85% yield in a 1 : 1 mixture. The methyl cuprate coupling reaction<sup>5</sup> was performed at room temperature overnight. The resulting methylated acetal was hydrolysed and oxidized to provide lactone (10) in 62% yield as a single isomer. The C-8  $\beta$ -methyl stereochemistry was realized by further transformation of this compound to iridomyrmecin and iso-iridomyrmecin. The stereochemistry could also be clarified indirectly by comparing it to the catalytic hydrogenation product of (13), in which the stereoselectivity is well understood.

<sup>‡</sup> All new compounds gave satisfactory spectroscopic and analytical data. Selected spectroscopic data for (7): <sup>1</sup>H NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  4.50–4.27 (3H, m), 2.63–2.36 (4H, m), 1.97–1.84 (1H, m), 1.83–1.71 (2H, m), 1.61–1.48 (1H, m); <sup>13</sup>C NMR ( $\text{CDCl}_3$ , 50 MHz)  $\delta$  173.7, 73.9, 66.5, 40.6, 35.1 ( $\times 2$ ), 34.0, 29.8. (8): m.p. 40–41 °C; <sup>1</sup>H NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  4.27 (2H, d, *J* 3.2 Hz), 4.00–3.88 (1H, m), 2.81–1.87 (7H, m), 1.33–1.19 (1H, m); *m/z*, 266 (15%, *M*<sup>+</sup>), 139 (73%, *M*<sup>+</sup>-I). (10): m.p. 40.5–42 °C; <sup>1</sup>H NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  4.27 (1H, dd, *J* 11.5, 4.3 Hz), 4.10 (1H, dd, *J* 11.5, 4.4 Hz), 2.70–2.52 (2H, m), 2.40–2.30 (1H, m), 2.03–1.97 (1H, m), 1.97–1.67 (3H, m), 1.30–1.07 (2H, m), 1.06 (3H, d, *J* 6.0 Hz); <sup>13</sup>C NMR ( $\text{CDCl}_3$ , 50 MHz)  $\delta$  173.6, 68.9, 44.5, 37.5, 34.8 ( $\times 2$ ), 34.6, 33.4, 18.7. (13): <sup>1</sup>H NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  5.07 (1H, q, *J* 2.0 Hz), 4.89 (1H, q, *J* 2.0 Hz), 4.33 (1H, dd, *J* 12, 6 Hz), 4.10 (1H, dd, *J* 12, 8 Hz), 3.01–2.90 (1H, m), 2.77–2.60 (2H, m), 2.41–2.22 (3H, m), 2.17–1.98 (1H, m), 1.50–1.38 (1H, m); <sup>13</sup>C NMR ( $\text{CDCl}_3$ , 50 MHz)  $\delta$  173.0, 150.6, 107.6, 69.1, 40.9, 34.7, 34.3, 33.2, 32.4; IR (neat), 1747  $\text{cm}^{-1}$ .

The hydroxy group of hydroxylactone (7) was protected as a silyl ether, followed by the lactone reduction to a hemiacetal and alcoholysis. Desilylation and oxidation gave ketone (11) in 51% yield (Scheme 2). Peterson alkenation<sup>6</sup> was carried out smoothly to provide alkene (12) in 89% yield. Acidic hydrolysis of acetal to hemiacetal gave a complex mixture. A 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) treatment<sup>7</sup> followed by pyridinium dichromate (PDC) oxidation, smoothly converted the acetal (12) to the alkenic lactone (13). Catalytic hydrogenation gave the  $\alpha$ -methyl compound, boschnialactone (3)<sup>8</sup> which exhibits different spectroscopic properties from those of compound (10). The retention of configuration during the methyl cuprate coupling reaction could be achieved via a single electron transfer.<sup>9</sup>

Lithium di-isopropylamide treatment of lactone (10), followed by addition of one equivalent of methyl iodide, provided a mixture of iridomyrmecin (1) and isoiridomyrmecin (2) which were separated by column chromatography and showed identical physical data to those reported in the literature.<sup>10</sup>

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