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

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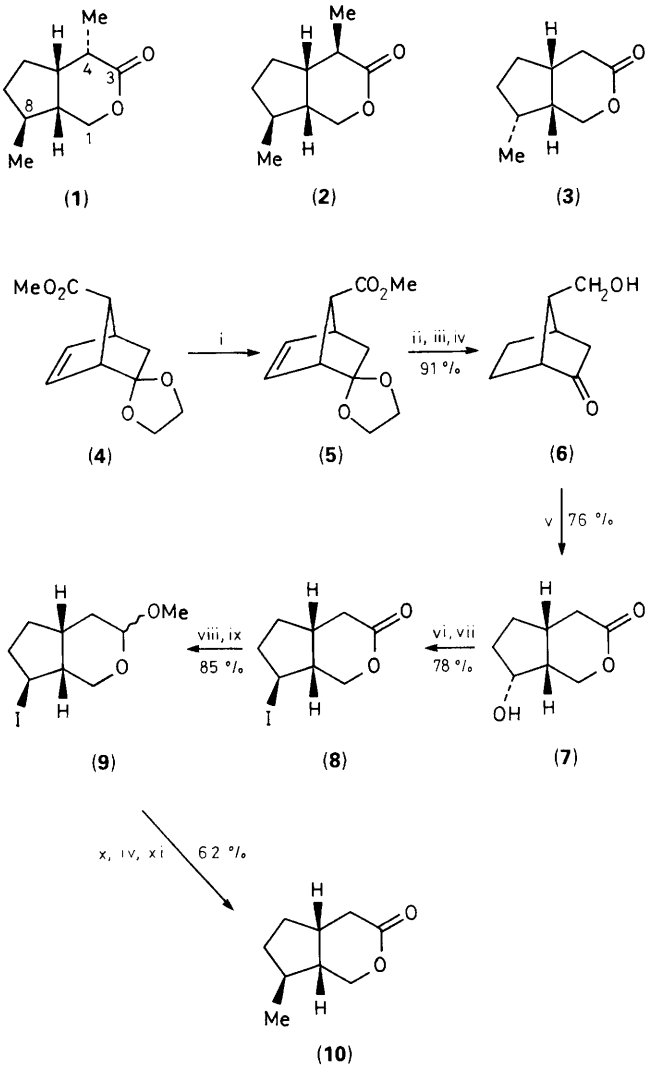
Stereocontrolled syntheses of iridomyrmecin, isoiridomyrmecin, and boschnialactone are accomplished through a Baeyer–Villiger oxidation and either a cuprate coupling reaction or catalytic hydrogenation.

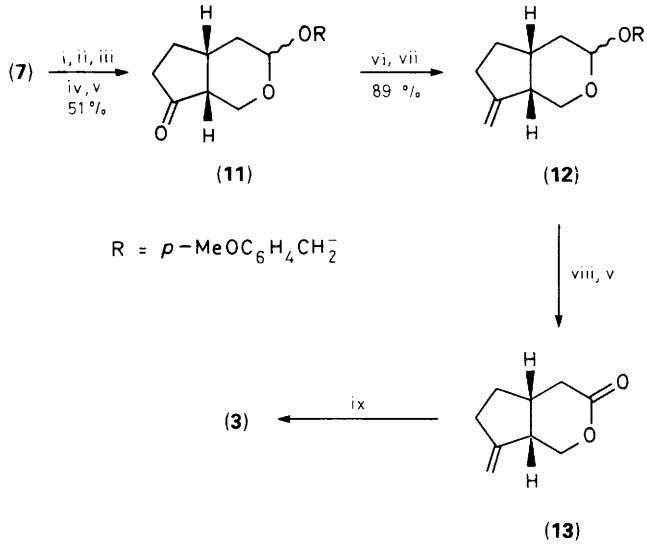
Insect repellents, iridomyrmecin (**1**), isoiridomyrmecin (**2**), and boschnialactone (**3**) are logical synthetic targets owing to their simple and well defined structures.[1] The cyclopentapyranone skeleton and the three contiguous non-epimerizable stereogenic centres are the focal point of the synthetic approaches.[2] 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, Pr^i_2NLi, THF, 0 °C, 30 min, then AcOH; ii, 10% Pd/C, H_2, EtOAc; iii, $LiAlH_4$, Et_2O; iv, toluene-*p*-sulphonic acid (*p*-TsOH), wet acetone; v, *m*-chloroperoxybenzoic acid, $NaHCO_3$, CH_2Cl_2; vi, $PhSO_2Cl$, 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, Et_2O, −78 °C to room temp., overnight; xi, PDC, CH_2Cl_2.

Acetal ester (**4**) (6 steps from 2,5-norbornadiene)[3] (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.† Catalytic hydrogenation, followed by a lithium aluminium hydride reduction and acetal hydrolysis, provided keto alcohol (**6**) in 91% yield. Baeyer–Villiger rearrangement[4] 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 transesterification occurs giving the desired cyclopentapyranone (**7**)‡ in 76% yield. The ^1H NMR spectrum of the corresponding acetate shows only one proton shift downfield [δ 5.27 (1H, q, *J* 6.3 Hz)] suggesting structure (**7**). Introduction of a *C*-8 β-methyl group was found to be troublesome. However, the problem was solved *via* a methyl cuprate coupling reaction and is described as follows.

† 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, Bu^tSiMe_2Cl, imidazole, 4-dimethylaminopyridine, CH_2Cl_2; ii, Dibal-H, THF; iii, 4-methoxybenzyl alcohol, *p*-TsOH, CH_2Cl_2; iv, Bu_4NF, THF; v, PDC, CH_2Cl_2; vi, Me_3SiCH_2Cl, Mg, Et_2O, then (**11**); vii, KH, THF; viii, DDQ, H_2O, CH_2Cl_2; ix, $(PPh_3)_3RhCl$, H_2, benzene.

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[5] 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 β-methyl stereochemistry was realized by further transformation of this compound to iridomyrmecin and isoiridomyrmecin. The stereochemistry could also be clarified indirectly by comparing it to the catalytic hydrogenation product of (**13**), in which the stereoselectivity is well understood.

‡ All new compounds gave satisfactory spectrosocpic and analytical data. *Selected spectroscopic data* for (**7**): ^1H NMR ($CDCl_3$, 200 MHz), δ 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); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.7, 73.9, 66.5, 40.6, 35.1 (×2), 34.0, 29.8. (**8**): m.p. 40—41 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 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^+), 139 (73%, M^+-I). (**10**): m.p. 40.5—42 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 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); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.6, 68.9, 44.5, 37.5, 34.8 (×2), 34.6, 33.4, 18.7. (**13**): ^1H NMR ($CDCl_3$, 200 MHz) δ 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); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.0, 150.6, 107.6, 69.1, 40.9, 34.7, 34.3, 33.2, 32.4; IR (neat), 1747 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[6] 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[7] followed by pyridinium dichromate (PDC) oxidation, smoothly converted the acetal (**12**) to the alkenic lactone (**13**). Catalytic hydrogenation gave the α-methyl compound, boschnialactone (**3**)[8] 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.[9]

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.[10]

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