Synthesis of (*cis*-6-Methyltetrahydropyran-2-yl)acetic Acid Involving the Use of an Organoselenium-mediated Cyclization Reaction

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A short stereospecific synthesis of (*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**1**) has been achieved from readily available starting materials using a novel organoselenium-mediated cyclization of alkenyl-substituted β-oxoesters.

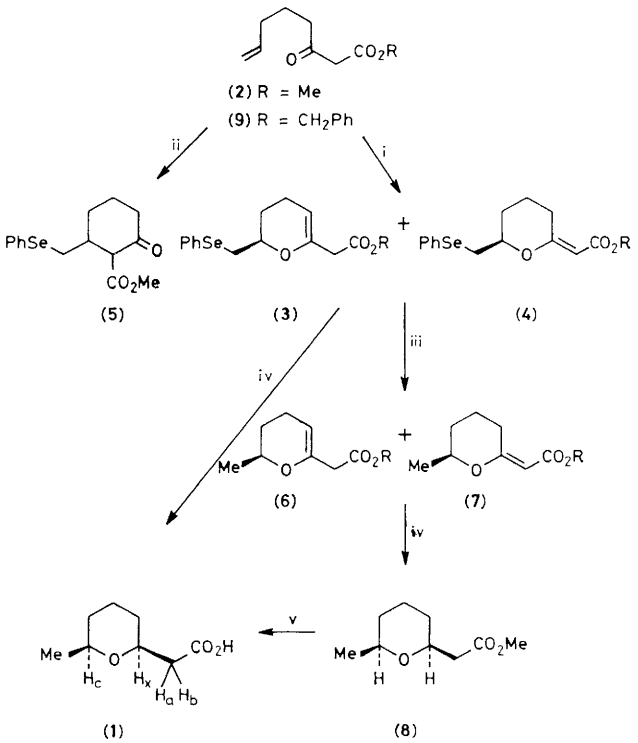
The use of organoselenium-mediated cyclizations to construct both hetero[1]- and carbo[2]-cyclic ring systems is now well recognised. Here we show how methodology developed in our laboratories[3] can be used efficiently to synthesise (*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**1**), a natural product recently isolated from *Viverra civetta*.[4]

The readily available alkenyl-substituted β-oxoester[5] (**2**) reacts at room temperature with *N*-phenylselenophthalimide (NPSP),[6] and trace amounts (0.01 equiv.) of tin tetrachloride to give a 9:1 mixture of compounds (**3**, R=Me) and (**4**, R=Me) in 84% combined yield. This mixture can be used directly in the next reaction; however, if conventional flash chromatography is used to purify the products, (**4**) is seen to rearrange to (**3**) which can be isolated in a pure form.† Treatment of (**2**) with NPSP and greater quantities of $SnCl_4$ (1 equiv.) results in the rapid formation of the carbocyclic product (**5**) in 83% yield.

Reduction of (**3**) and (**4**) with tri-n-butyltin hydride[7] proceeds well, without ring opening, to give (**6**, R=Me) and (**7**, R=Me) in 64% yield. Upon similar treatment, pure (**3**) gave (**6**) in comparable yield.

Hydrogenation of (**6**) and (**7**) using Raney-nickel as a catalyst gave a single compound shown to be methyl (*cis*-6-methyltetrahydropyran-2-yl)acetate (**8**) in 71% yield. This ester was identical with the previously synthesised material.[4] Hydrolysis of (**8**) gave a 92% yield of (*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**1**)[4,8] [m.p. 51—52 °C; ^{1}H n.m.r. δ 10.1 (1H, br.s, CO_2H), 3.84—3.72 (1H, m, H_X), 3.53 (1H, m, H_C), 2.9 (1H, q, H_b, J_{ab} 15, J_{bx} 7.5 Hz), 2.48 (1H, q, H_a, J_{ab} 15 Hz), 1.9—1.15 (6H, m), and 1.19 (3H, d, *J* 6.3 Hz)].

In an effort to simplify this route further we chose to combine the two reduction steps with a final deprotection reaction.



Scheme 1. *Reagents and conditions:* i, NPSP–$SnCl_4$ (1.1:0.01), room temp., CH_2Cl_2, 2 h; ii, NPSP–$SnCl_4$ (1.1:1.0), room temp., CH_2Cl_2, 30 min; iii, Bu^n_3SnH, azoisobutyronitrile, toluene, heat, 1 h; iv, H_2–Raney-nickel, 100 atm, EtOH, 60 °C, 20 h; v, 10% NaOH, MeOH–H_2O, heat, 15 min.

Thus, when the benzyl-substituted compound (**9**) was treated with NPSP–$SnCl_4$ (1.1:0.01 equiv.) as before, a 4:1 mixture of (**3**, R=CH_2Ph) and (**4**, R=CH_2Ph) was obtained in 57%

† All new compounds were fully characterised by spectroscopic and microanalytical methods.

yield. This mixture, on reduction with H_2–Raney-nickel, afforded (**1**) in one step in an unoptimised 47% yield.

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