Synthesis of Substituted Dioxabicyclo[*n*.2.1]alkanes through Palladium Catalysed Oxidative Cyclisation

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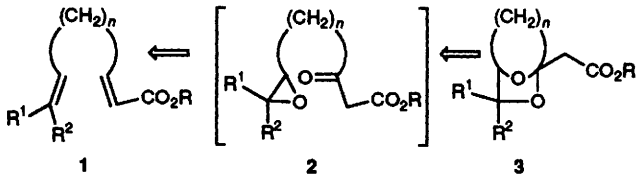
Epoxy α,β-unsaturated esters derived from diene-ester **1** underwent one-pot regioselective oxidative cyclisation to form substituted dioxabicyclo[*n*.2.1]alkanes in the presence of Na_2PdCl_4, Bu^tO_2H–aq. acetic acid in good yield.

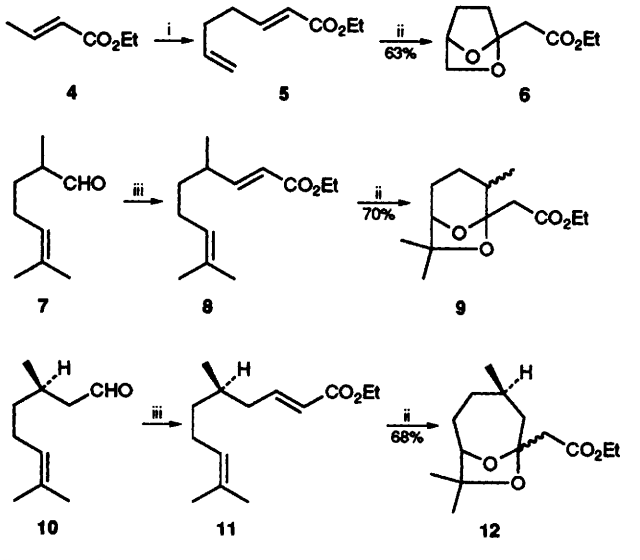
Palladium catalysed reactions have emerged as excellent synthetic alternatives for a variety of useful compounds. Recently the palladium mediated cyclisation reactions have attracted much attention and a number of reports have appeared in which the use of various catalyst systems like Pd-ferrocenylphosphine complex,[1] $Pd(PPh_3)_4$,[2] $LiPdCl_3$,[3] $Pd(OAc)_2$,[4] Pd-bis(acetonitrile)dichloride[5] *etc.* has been described.

Dioxabicyclo[*n*.2.1]alkanes form the basic skeleton of various natural products like insect pheromones[6] *viz*. Brevicomin, Multistriatin, Frontalin *etc.*, and also serve as key synthetic intermediates for a number of biologically active marine natural products containing medium and large sized cyclic ether derivatives.[7,8] In view of the importance of these dioxabicyclic structures we report herein a novel and convenient method for constructing these skeletons using a one-pot synthetic strategy. The key reaction involves palladium catalysed formation of β-ketoester and subsequent intramolecular ketalisation of an unisolated epoxy ketone intermediate (Scheme 1).

The oxidation of α,β-unsaturated esters to corresponding β-ketoesters using sodium–palladium tetrachloride catalyst has been reported by Tsuji *et al.*[9] This rather unexploited reaction was selected for our trials. Moreover the catalyst Na_2PdCl_4 can readily be prepared by heating a mixture of palladium chloride and an excess of sodium chloride in water for a few minutes.



Scheme 1



Scheme 2 *Reagents and conditions*: i, NaH, THF, CH_2=CH–CH_2Br, 50°C; ii, (a) MCPBA, chloroform, 0–10°C, 1 h; (b) Na_2PdCl_4, Bu^tO_2H, 50% aq. acetic acid, 50–60°C, 2–3 h; iii, Ph_3P=$CHCO_2Et$, toluene, reflux, 8 h

The required conjugated diene-ester **5** was prepared by the reaction of ethyl crotonate with allyl bromide in the presence of sodium hydride in dry THF, Scheme 2. The esters **8** and **11** were synthesised from 2,6-dimethyl-5-heptenal and citronellal respectively through Wittig reaction with triphenylethoxycarbonylmethylene phosphorane.[10] The selective epoxidation of the isolated double bond in the esters with *m*-chloroperbenzoic acid (MCPBA) followed by treatment with Na_2PdCl_4 and *tert*-butyl hydroperoxide in 50% aq. acetic acid at 50–60°C afforded the substituted 5,7-dioxabicyclo[2.2.1]heptane **6**, 6,8-dioxabicyclo[3.2.1]octane **9** and 7,9-dioxabicyclo-[4.2.1]nonane **12** in 63, 70 and 68% yields, respectively.† Evidently these compounds were formed through the cyclisation of epoxy-β-ketoester intermediate **2** generated *in situ*. *tert*-Butyl hydroperoxide acts as the reoxidant of Pd^0 in the reaction.

A typical reaction procedure involves the addition of MCPBA to a stirred solution of the diene-ester in chloroform at 0–10°C. The epoxide formation was checked by TLC. After one hour, the chloroform was removed under vacuum and the crude residue was treated directly with a mixture of Na_2PdCl_4 (0.2 mmol), Bu^tO_2H (1.5 mmol) and 50% aqueous acetic acid (10 ml) at 50–60°C for 2–3 h.‡ The reaction mixture was extracted with ethyl acetate, washed with sodium metabisulfite, brine and dried over anhydrous sodium sulfate. Removal of solvent followed by column chromatography on silica gel gave the required product in the yield mentioned above.

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Footnotes

† Elemental analyses and spectral data of all new compounds are in accordance with the structures assigned. Selected data for compounds **5**, **6**, **8**, **9**, **11** and **12** are as follows: **5**: IR ν_{max}/cm^{-1} 1730, 1640, 1370; ^1H NMR (60 MHz, $CDCl_3$) δ 1.30 (t, 3H, *J* 7 Hz), 4.20 (q, 2H, *J* 7 Hz), 5.15 (br m, 2H), 5.95 (d, 1H, *J* 8 Hz), 6.05 (dd, 1H, *J* 8 and 16 Hz); MS (*m*/*z*); 154(M^+). **6**: IR ν_{max}/cm^{-1} 1730, 1370; ^1H NMR (60 MHz, $CDCl_3$) δ 1.25 (t, 3H, *J* 7 Hz), 2.60 (br s, 2H), 3.30 (m, 2H), 4.10 (q, 2H, *J* 7 Hz), 4.30 (m, 1H); MS (*m*/*z*): 186(M^+).

8: IR ν_{max}/cm^{-1} 1725, 1640, 1380, 1370; ^1H NMR (60 MHz, $CDCl_3$) δ 1.06 (d, 3H, *J* 7 Hz), 1.30 (t, 3H, *J* 7 Hz), 1.60 (s, 3H), 1.70 (s, 3H), 4.20 (q, 2H, *J* 7 Hz), 5.10 (br t, 1H, *w*/2 12 Hz) 5.75 (d, 1H, *J* 16 Hz), 6.90 (dd, 1H, *J* 8 and 16 Hz); MS (*m*/*z*): 210(M^+). **9**: IR ν_{max}/cm^{-1} 1735, 1460, 1370; ^1H NMR (60 MHz, $CDCl_3$) δ 0.85 (d, 3H, *J* 7 Hz), 1.25 (t, 3H, *J* 7 Hz), 1.25 (s, 3H), 1.36 (s, 3H), 2.71 (s, 2H), 3.95 (br s, 1H), 4.20 (q, 2H *J* 7 Hz); MS (*m*/*z*): 242(M^+).

11: IR ν_{max}/cm^{-1} 1720, 1650, 1370; ^1H NMR (60 MHz, $CDCl_3$) δ 0.95 (d, 3H, *J* 6 Hz), 1.30 (t, 3H, *J* 7 Hz), 1.62 (s, 3H), 1.69 (s, 3H), 4.20 (q, 2H, *J* 7 Hz), 5.10 (br t, 1H, *w*/2 12 Hz), 5.82 (d, 1H, *J* 15 Hz), 6.95 (m, 1H); MS (*m*/*z*): 224(M^+). **12**: IR ν_{max}/cm^{-1} 1730, 1470, 1380; ^1H NMR (60 MHz, $CDCl_3$) δ 0.95 (d, 3H, *J* 6 Hz), 1.25 (t, 3H, *J* 7 Hz), 1.40 (s, 6H), 2.55 (br s, 2H), 4.15 (q, 2H, *J* 7 Hz), 4.20 (t, 1H, *J* 6 Hz); MS (*m*/*z*): 256(M^+).

‡ The cyclisation of the unisolated epoxy ketones to compounds **8** and **9** was found to be completed within 2–3 h, whereas the formation of cyclic compound **12** was completed in 10–12 h.

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