A Radical Cyclisation Route to α-Methylene-γ-butyrolactones

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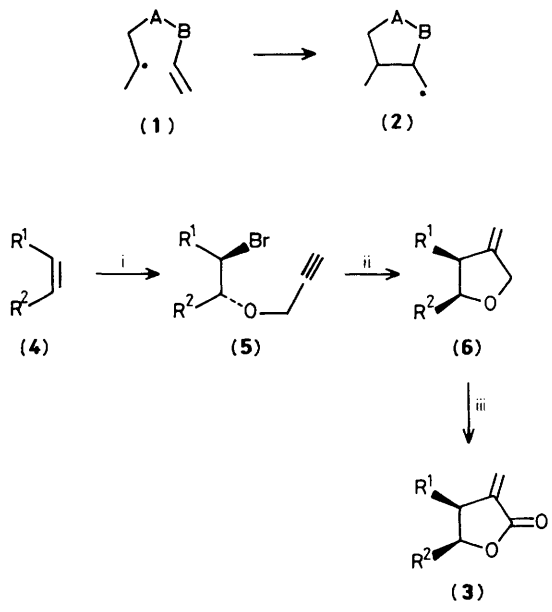
A three-step synthesis of α-methylene-β-butyrolactones is described, *via* radical cyclisation of 2-bromoalkyl prop-2-ynyl ethers (**5**) to 3-methylenetetrahydrofurans (**6**) using a tin catalyst.

The use of free radical intermediates in ring formations has until recently been limited to studies of a more mechanistic bias. However radical cyclisation is now finding a place in organic synthesis, by virtue of its stereo- and regio-specific nature, *e.g.* (**1**) → (**2**), in the construction of five membered rings.[1] In our quest for a general methodology to construct α-methylene-γ-butyrolactone (**3**) a widely occurring biologically important moiety,[2] we opted to use radical cyclisation as the key step. We now report our preliminary findings which have culminated in a three-step entry to (**3**) starting from alkenes.

The methodology is depicted in Scheme 1; radical cyclisa-



a; R^1, R^2 = $-[CH_2]_4-$
b; R^1, R^2 = $-[CH_2]_6-$
c; R^1, R^2 = $-[CH_2]_3O-$
d; R^1 = H, R^2 = $[CH_2]_8CO_2Me$

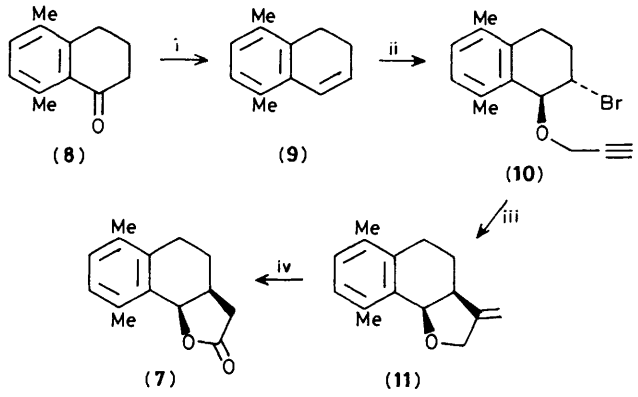
Scheme 1. *Reagents:* i, NBS, $HC{\equiv}CCH_2OH$; ii, Bu^n_3SnCl, $NaCNBH_3$, AIBN, Bu^tOH, 5—7 h; iii, PDC, DMF.

Table 1. Synthesis of 3-methylenetetrahydrofurans from alkenes *via* radical cyclisation.[a]

Alkene	Cyclisation product	Cyclisation yield (%)	Oxidation[b] yield (%)
(**4a**)	(**6a**)	96	60
b	**b**	68[c]	48
c	**c**	97	—[d]
d	**d**	92	55

[a] All compounds were purified by silica gel column chromatography and gave satisfactory analytical and spectral data. Yields refer to the isolated and chromatographically pure compounds. [b] Oxidations were carried out using 10 equiv. of PDC in DMF for 24 h at room temperature. [c] In addition 25% of the reduction product, cyclo-octyl prop-2-ynyl ether, was also obtained. [d] Starting material recovered under the conditions.

tion of the bromo propynyl ether (**5**) generates 3-methylenetetrahydrofuran (**6**), which on allylic oxidation leads to (**3**). The starting bromopropynyl ethers (**5**) were obtained by *N*-bromosuccinimide (NBS) bromination of alkenes in the presence of prop-2-ynyl alcohol in over 80% yield.[3] The cyclisation of (**5**) can be carried out by refluxing a 0.02 M solution in benzene with 1.1 equiv. of Bu^n_3SnH in the presence of a catalytic amount of azoisobutyronitrile (AIBN), but was achieved more conveniently using Bu^n_3SnH generated *in situ* (Bu^n_3SnCl–$NaCNBH_3$). In a typical experiment, 1 mmol of (**5**) was refluxed with 0.1 mmol of Bu^n_3SnCl, 1.5 mmol of sodium cyanoborohydride, and a catalytic amount of AIBN in 15 ml of Bu^tOH for 5—7 h followed by the usual work-up and purification by silica gel column chromatography. The cyclisation proceeded smoothly in all cases (Table 1) except that of the cyclo-octane series, where a considerable amount (25%) of the reduction product, cyclo-octyl prop-2-ynyl ether, was obtained along with (**6c**). Of the various oxidation conditions attempted, we found it most convenient to use pyridinium dichromate (PDC) in dimethylformamide (DMF). The yields of cyclisation and oxidation products are summarised in Table 1.



Scheme 2. *Reagents:* i, $NaBH_4$ then PPTs; ii, NBS, $HC{\equiv}CCH_2OH$–CH_2Cl_2; iii, Bu^n_3SnCl, $NaCNBH_3$, AIBN, Bu^tOH; iv, PDC (excess), DMF.

We then applied this methodology to the synthesis of an analogue of santonin,[4] 11,13-dehydroisohyposantonin (**7**), starting from the readily available 5,8-dimethyltetralone (**8**) as shown in Scheme 2. Thus, sodium borohydride reduction of (**8**) followed by pyridinium toluene-*p*-sulphonate (PPTs) catalysed dehydration furnished alkene (**9**) in >95% yield. Bromination of (**9**), as expected, with NBS in prop-2-ynyl alcohol–CH_2Cl_2 regiospecifically furnished the bromo ether (**10**).† The key cyclisation of (**10**) to (**11**) proceeded in 85% yield under standard conditions in a stereospecific manner. The spectral data† for (**11**) are consistent with its formulation and in particular the signal at δ 4.7 (d, *J* 5 Hz) confirms the *cis* ring junction (for *trans* the coupling constant is known to be 9 Hz).[5] Finally oxidation of (**11**) with excess of PDC in DMF generated the lactone (**7**).

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† *Selected spectral data* for (**10**): i.r. ($CHCl_3$) 3300, 2150 cm^{-1}; ^1H n.m.r. (CCl_4) δ 6.86 (2H, s), 4.73 (2H, m), 4.2 (2H, d, *J* 3 Hz), 2.6 (2H, m), 2.37 (1H, t, *J* 3 Hz), 2.3 (3H, s), 2.16 (3H, s), 2.2 (2H, m). (**11**): i.r. (neat) 3060, 880 cm^{-1}; ^1H n.m.r. (CCl_4) δ 6.8 (2H, s), 5.0 (1H, m), 4.88 (1H, m), 4.7 (1H, d, *J* 5 Hz), 4.25 (2H, m), 2.4 (3H, m), 2.3 (3H, s), 2.14 (3H, s), 1.75 (2H, m). (**7**): i.r. (neat) 1760, 910 cm^{-1}; ^1H n.m.r. (CCl_4) δ 6.85 (2H, s), 6.1 (1H, d, *J* 2 Hz), 5.55 (1H, d, *J* 2 Hz), 5.37 (1H, d, *J* 6.5 Hz), 3.1 (1H, m), 2.5 (2H, m), 2.4 (3H, s), 2.2 (3H, s), 1.8 (2H, m).