A New Synthetic Route to β-Bromoprop-2-ynyl Mixed Acetals and Bromovinyl Bis-allyl Mixed Acetals, Precursors of α-Methylene-γ-Butyrolactones

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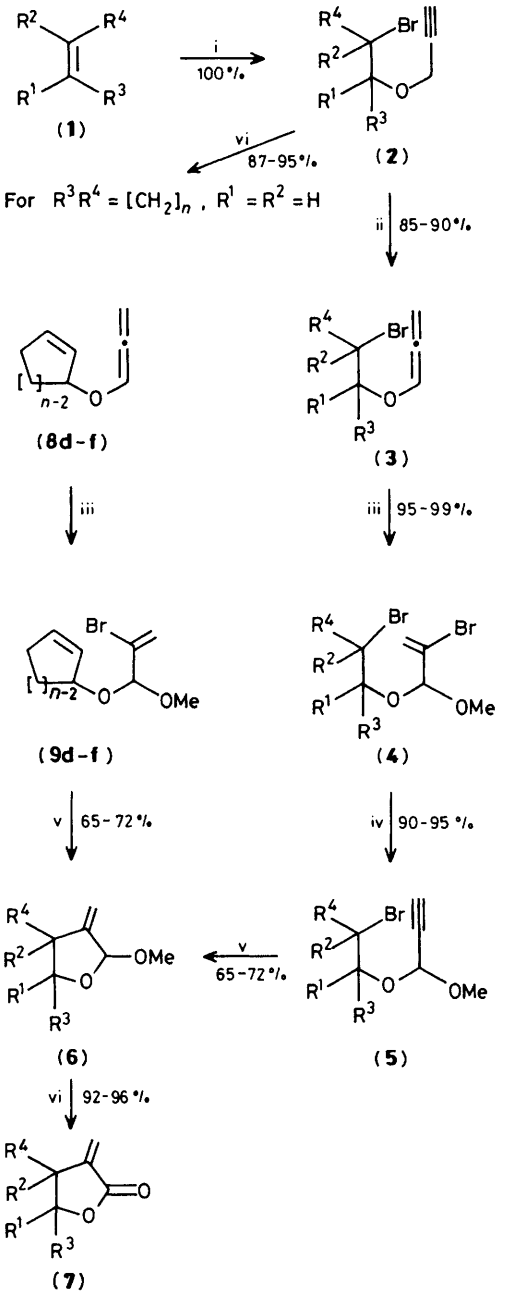
Cohalogenation by *N*-bromosuccinimide in methanol of β-bromoallenyl ethers (**3a—g**) or allyl allenyl ethers (**8d—f**) affords unsaturated halogeno-compounds (**5a—g**) or (**9d—f**) which are converted *via* homolytic carbocyclization into α-methylene-γ-butyrolactones (**7a—g**).

There has been considerable work on the synthesis of α-methylene-γ-buytrolactones owing to the biological and tumour-inhibiting activities of a number of naturally occurring terpenoids containing this structural unit.[1] More specifically, methylene-tetrahydrofurans have recently received much attention owing to their preformed methylene moiety.[2] They can readily be synthesized by radical cyclization of β-bromoprop-2-ynyl ethers, then oxidized into α-methylene-γ-butyrolactones, but the low yield of the last step limits the usefulness of this synthetic approach.[3]

In order to enlarge the scope of this procedure, a characteristic of which is the regio- and stereo-selectivity of the intramolecular free-radical cyclization step,[4] we have extended the reaction to β-bromoprop-2-ynyl mixed acetals (**5a—g**) and bromovinyl bis-allyl mixed acetals (**9d—f**).

Halogenation of the alkenes (**1**) by *N*-bromosuccinimide (NBS) in prop-2-ynyl alcohol afforded the β-bromopropynyl ethers (**2**) in almost quantitative yields (Scheme 1), the reaction being regio- and stereo-selective for compounds (**2a,b,g**). The propynyl acetals (**5**) could easily be prepared from the ethers (**2**) in three steps: the allenyl ethers (**3**) were formed by the reaction of (**2**) with a catalytic amount of Bu^{t}OK in benzene or pentane (4—6 h);[6] bromination–dehydrobromination led to the acetals (**5**) *via* the dibromides (**4**).

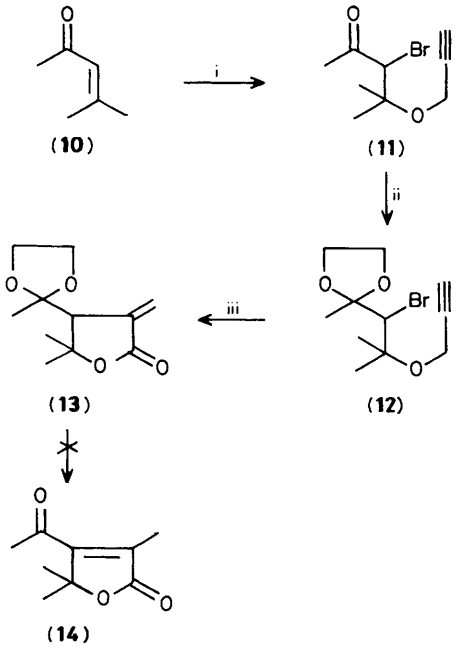
For the cyclic derivatives (**2d—f**), on the other hand, treatment with 1.2 equivalents of Bu^{t}OK in refluxing benzene



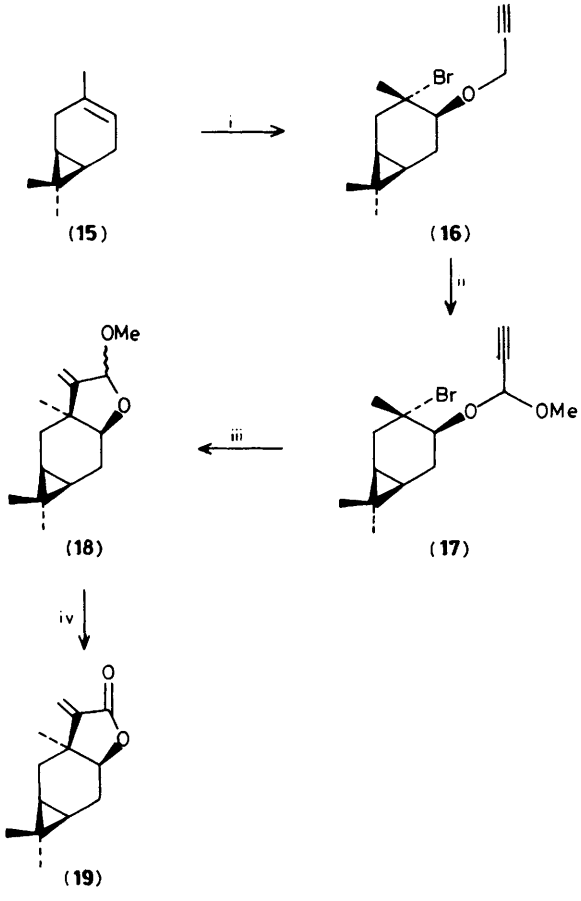
	R¹	R²	R³	R⁴
a	Me	H	Me	H
b	Me	Me	Me	H
c	Me	Me	Me	Me
d	H	H	—[CH₂]₃—	
e	H	H	—[CH₂]₄—	
f	H	H	—[CH₂]₅—	
g	Me	H	—[CH₂]₄—	

The bicyclic compounds (**7d—g**) are *cis*-ring fused.

Scheme 1. *Reagents and conditions:* i, HC≡C–CH_2OH, NBS (0 °C; 1 h); ii, Bu^{t}OK (catalytic quantity), pentane or C_6H_6, 4—6 h; iii, add NBS (1.0 equiv.) in Me_2CO to (**3**) or (**8**) in MeOH, −40 °C, 0.5 h; iv, Bu^{t}OK (1.1 equiv.), pentane, room temp.; v, (**5**) or (**9**), 10 mmol, 0.35 M in C_6H_6, Bu_3SnH (1.25 equiv.), azoisobutyronitrile (AIBN) catalyst, C_6H_6, 2 h, reflux.



Scheme 2. *Reagents and conditions:* i, HC≡CCH_2OH, NBS; ii, $ClSiMe_3$, $HOCH_2CH_2OH$; iii, (a), Bu^{t}OK (cat. amount), pentane, room temp.; (b), NBS, MeOH; (c), Bu_3SnH, AIBN, C_6H_6; (d), Jones reagent.



Scheme 3. *Reagents and conditions:* i, HC≡CCH_2OH, NBS; ii, Bu^{t}OK (cat. amount), pentane, room temp.; iii, Bu_3SnH, AIBN, C_6H_6; iv, *m*-$ClC_6H_4CO_3H$, BF_3–Et_2O.

for 3 h afforded the allyl allenyl ethers (**8d—f**), treatment of which in acetone with NBS at −40 °C gave the mixed acetals (**9d—f**). Intramolecular free-radical cyclization of either the propynyl acetals (**5a—g**) or the bromovinyl acetals (**9d—f**) by heating the Bu_3SnH in refluxing benzene in the presence of azoisobutyronitrile (AIBN) gave the 2-methoxy-3-methylene-tetrahydrofurans (**6**) (65—72%). Jones oxidation of (**6**) gave the α-methylene-γ-lactones (**7**) in 92—96% yields.

It is noteworthy that the α-methylene-γ-lactones (**7d—f**) can be obtained in only five steps *via* (**8**) from starting cyclic alkenes in at least 50% overall yield.

The presence of an additional oxygen function in the homoallylic position is assumed to enhance tumour-inhibiting activities of α-methylene-γ-lactones.[1d,e] Thus mesityl oxide (**10**) was a suitable starting material for preparing the oxygenated α-methylene-γ-butyrolactone (**13**) (Scheme 2). Favorskii-type rearrangements could be avoided by converting (**11**) into the ethylene acetal[7] (**12**). The protected carbonyl group prevents the isomerization of (**13**) to give (**14**).[2,8]

Starting from Δ^3-carene (**15**), the acid sensitive α-methylene-γ-lactone (**19**) ($[\alpha]_{578}^{20}$ 68.5°, *c* 7.3, methanol) could be prepared similarly using mild oxidation conditions.[9] The regio- and stereo-selectivity of the cohalogenation to give (**16**) and the free-radical cyclization lead to diastereospecificity in the product (**19**)[10] (Scheme 3).†

Compounds of type (**9**) have previously been prepared by a more elaborate synthetic route involving addition of butoxyallene to an excess of allylic alcohol.[10] Our procedure which requires only readily available starting materials such as the alkenes (**1a—g**) and (**15**) or the α,β-unsaturated carbonyl compound (**10**) and prop-2-ynyl alcohol, appears to be as efficient as others which have already been reported.[1a, 11]

Reveived, 18th May 1987; Com. 657

† (**19**): N.m.r. ($CDCl_3$, 200 MHz): ^1H: δ 0.43—0.97 (m, 2H), 1.07 (s, 6H), 1.43 (s, 3H), 2.43—3.13 (m, 5H), 5.5 (d, *J* 2.5 Hz, 1H), and 6.08 (d, *J* 2.5 Hz, 1H); ^{13}C: δ 169.9, 140.3, 122.5, 84.5, 44.7, 30.6, 28.9, 28.2, 26.5, 20.6, 19.8, 19.2, and 14.7.

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