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Facile Construction of Substituted Bicyclo [n.3.1] Alkanones and the Synthesis of a 12-Membered Dilactone via a New Functionalized Pentadienoic Ester[1]

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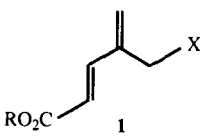
Abstract: 4-Hydroxymethyl-2,4-pentadienoate was effectively synthesized and used for a synthetic entry to keto bridged bicyclo [n.3.1] alkanones and for the synthesis of a 12-membered macrodilide characterized by two *trans* double bonds, part of two vinylogous α-methylene lactone units.

2,4-Pentadienoic esters **1**, in which the C-4 methyl substituent is functionalized by a group (X) able to promote nucleophilic or electrophilic reactivity, are compounds of potential synthetic interest due to the presence of several reactive centers. We report a convenient approach to **1** and reveal the utility of such

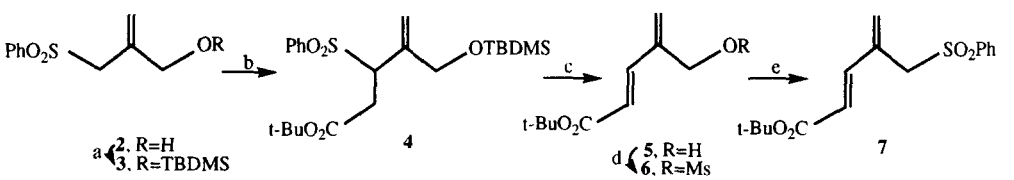


1

compounds as building blocks in synthesis.[2] Preparation of **1** (X=Br), via allylic bromination of 4-methyl-2,4-pentadienoates, failed in our hands, the latter being unreactive towards NBS even under the drastic conditions used previously on structurally similar compounds.[3]

We have devised a short and convenient synthesis of the hydroxyester **5** starting from the readily

Scheme 1

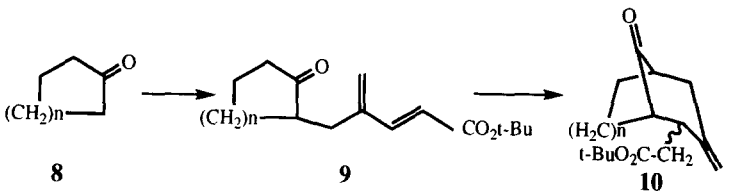


[a]TBDMSCl, imidazole, DMF, RT, 88%; [b]BuLi (1.2 eq), THF, -78°C, 10 min. then HMPA (1.1 eq), $BrCH_2CO_2t$-Bu (1.1 eq), 0.5h, -78°C, 85%; [c]TBAF, RT, 1h, 89%; [d]CH_2Cl_2, Et_3N, DMAP (cat),MsCl, 0°C, 0.5h, 91%, [e]$PhSO_2Na$,DMF, RT, 1.5h, 80%.

available hydroxysulfone **2**[4] (Scheme 1). Protection as the silyl ether **3** was followed by alkylation with *t*-butyl bromoacetate to give **4** in excellent yield. Deprotection with tetrabutylammonium fluoride (TBAF) led to

TABLE

The synthesis of bicyclo [n.3.1] alkanones



8 **9** **10**

8	**9**(isolated yield)	**10**(isolated yield), *endo:exo*
n=1	75%[b]	75%[e], 86:14
n=2	82%[c]	89%[f], 100:0
n=3	78%[c]	74%[g], 60:40[h]
n=4	70%[d]	67%[f], 60:40[h]

[a].For general conditions see footnotes 6 and 7; [b] 5h, -78°C. [c]0.5h, -78°C then 1.5 h, -40°C; [d] 2h, -78°C; [e] -5° C, 15 min; [f] 0°C to RT, 1h, [g] 0°C to RT, 2.5h; [h] Inseparable stereoisomeric mixture.

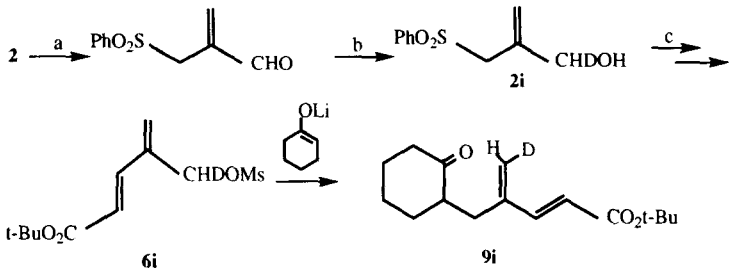
concomitant sulfone elimination to afford (E)-4-hydroxymethyl-2,4-pentadienoate **5**.[5] Further conversion to the mesylate **6** enabled its utilization as an effective building block for the construction of bicyclic keto bridged systems. Thus, lithium enolates of cycloalkanones (**8**, n=1-4), reacted readily with the mesylate **6** to afford products **9**,[5,6] which underwent regioselective intramolecular conjugate addition under basic conditions (*t*-BuOK, *t*-BuOH-THF, 1:1) to give the bicyclo[n.3.1]alkanones **10** (Table).[7,8] The two-step sequence **8** →**10** was also performed as a tandem process in one operation by adding *t*-BuOK in *t*-BuOH to the reaction mixture containing **9**, but the overall yield by this procedure was lower (40%, for n=2). We assume that the first step (**8** →**9**) involves a conjugate addition enhanced by the elimination of the mesylate group, rather than a S_N2 or S_N2' process. Indeed, **9** (n=2) could also be obtained by substituting mesylate **6** with sulfone **7**, under identical conditions.

The direction of attack of cycloalkanone enolates on **6** was independently confirmed by the preparation of the deuterated mesylate **6i** via hydroxysulfone **2i**: the ultimate product **9i** was found to be deuterated exclusively in the vinyl group, as evidenced by ^1H NMR (Scheme 2).

The *endo-exo* ratio for the side chain configuration, as established by help of ^1H NMR allylic coupling between the exocyclic methylene protons and the methine proton at the stereogenic center, was found to be dependent on the ring size of the cycloalkanone. Ambiguities concerning the preferred conformation of larger ring size substituted cycloalkanones are possibly the cause for the lack of stereoselectivity in **10**, when n=3 and n=4[9]. This rapid synthetic entry to bicyclic bridged systems should be useful for the construction of terpenoids in which such units are prevalent[10] and can be utilized for the elaboration of larger rings by the excision of the keto bridge.[11]

Next, hydroxyester **5** was successfully utilized for the synthesis of the dilactone **16**. (Scheme 3). The hydroxyl group in **5** was protected as the *t*-butyldiphenylsilyl ether (**11**) which was sufficiently resistant on

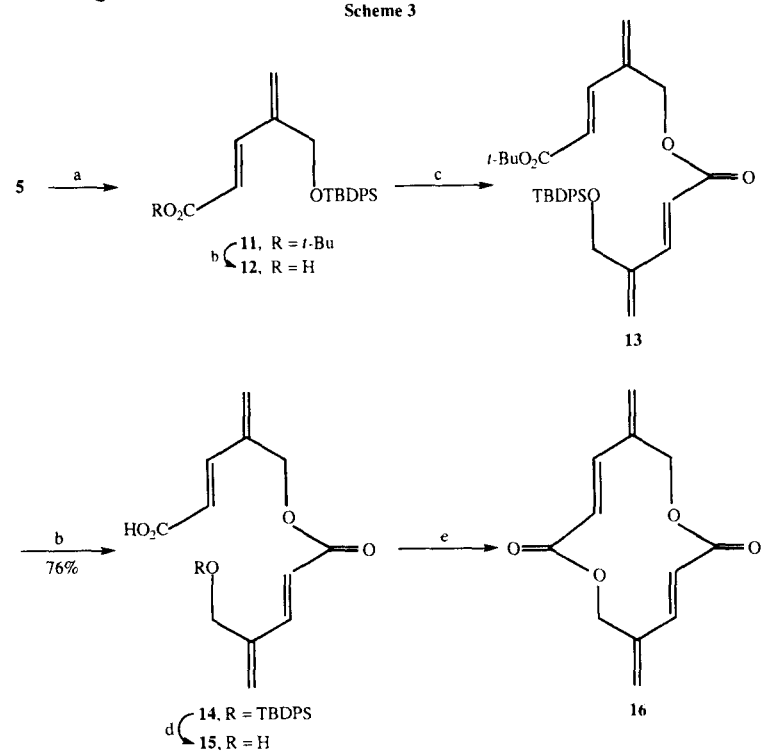
Scheme 2



[a] Jones reagent, 0°C; [b] $NaBD_4$, $CeCl_3$ $7H_2O$, EtOH, 0°C; [c] See Scheme 1.

subsequent treatment with trifluoroacetic acid to afford **12**. Esterification of the latter with the hydroxyester **5** gave the dimeric ester **13**. Cleavage of the *t*-butyl ester to give **14** was followed by the deprotection of the hydroxyl group affording the hydroxyacid **15**,[5] which underwent smooth cyclization under Mitsunobu conditions[12] to provide (3E, 9E)-5,11-dimethylene-1,7-dioxacyclododeca-3,9-diene-2,8-dione (**16**). NMR spectral evidence indicates that the dilactone has a center of symmetry[13] with an unchanged conformation even at -80°C. Though models indicate the possibility of *s-cis* or *s-trans* conformations, the NOE data are consistent only with a *s-trans* arrangement of the two diene moieties.[14].

Scheme 3



[a]TBDPSCl (1.1 eq.), imidazole, DMF, 1.5 h 94%; [b]TFA(5 eq) CH_2Cl_2, RT, 16 h 72%; [c]**5**(1.1 eq), DCC (1.2 eq), DMAP (10 mol %) CH_2Cl_2, RT, 0.5 h, 70%; [d]TBAF (1.1 eq), THF, RT, 2h, 73%; [e]Ph_3P (1.1 eq) DEAD (1.2 eq) THF, 1.5 h, RT, 81%.

The structure of **16** is interesting by comprising two *trans* double bonds in a 12-membered ring and two vinylogous α-methylene lactone structural units, thus justifying further exploration of its biological and chemical properties.[15]

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References and Notes.

1. Synthetic Methods 42. For paper 41 see Belostotskii, A., Hassner, A., *Tetrahedron Lett.* **1994**, *35*, 3075.
2. We are aware of a single synthesis of a 2,4-pentadienoate with a functionalized C-4 methyl substituent (**1**, X=OTBDMS) by a non selective, low-yield route: Lai, M-t.; Ding, L.; Oh, E.; Liu, H-w. *J. Am. Chem. Soc.* **1993**, *115*, 1619.
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5. All new compounds were fully characterized by ^{1}H and ^{13}CNMR and by MS analysis.
6. A typical procedure involves adding the ketone (1.5 eq) in THF to a stirred solution of LDA in THF (1.3 eq) at -78°C; the temperature of the mixture was increased to -20°C (0.5h) then cooled again to -78°C and the mesylate (1 eq) in THF was added dropwise; for time and temperature in specific reactions see Table; the reaction was quenched by pouring into 5% aqueous HCl and extracted with ether.
7. In a typical procedure freshly prepared *t*-BuOK in *t*-BuOH (1.5 eq) was added to **9** (1 eq) dissolved in *t*-BuOH-THF at 0°C, with the resulting ratio 1:1 of the solvents; for time and temperature in specific reactions see Table. The reaction was quenched with 5% aqueous HCl and extracted with ether.
8. For an α, α' annelation of the pyrrolydinenamine of a cyclohexanone derivative by use of 2-bromomethylacrylate, see Stetter H.; Thomas H.G., Meyer K. *Chem. Ber.* **1970**, *103*, 863.
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12. For a review see Hughes, D.L. *Org. React.* **1992**, *42*, 355.
13. ^{1}H-NMR (300-MHz, $CDCl_3$): δ 4.80 (2H, s), 5.71 (2H, s), 6.00 (1H, d, *J*=16 Hz), 7.39 (1H, d, *J*=16 Hz). The spectrum was recorded also in C_6D_6 because of the unexpected appearance of the *exo*-methylene protons as a singlet in $CDCl_3$ (δ 5.71): δ 4.54 (2H, s), 4.97 (1H, s), 5.05 (1H, s), 6.08 (1H, d, *J*=16 Hz), 7.40 (1H, d, *J*=16Hz); ^{13}C-NMR (75-MHz, $CDCl_3$): 64.69 (t), 119.54 (d), 129.37 (t), 139.21 (s), 144.36 (d), 166.51 (s). MS: (EI) m/z = 220, 219, 202, 190, 175, 110, 94; HRMS.
14. NOE experiments (in C_6D_6) showed strong enhancement between one of the protons of the *exo*-methylene group and the β-proton of the enone subunit, but no such effect was observed with the α-proton of the enone.
15. See e.g., Keck, G.E., Boden, E.P., Wiley, M.R. *J. Org. Chem.* **1989**, *54*, 896 for examples of biologically active unsaturated macrocyclic dilactones.

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