Total Synthesis of (±)-Myodesmone employing a Regiospecifically Substituted α-Oxoketene Dithioacetal

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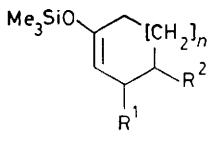
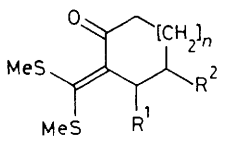
The α-oxoketene dithioacetal (**2a**) has been prepared in good yield and converted in four steps to (±)-myodesmone (**6**) in the first synthesis of this furanosesquiterpene.

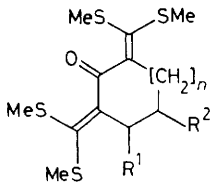
The α-oxoketene dithioacetal functionality may be viewed as either a β-ketoester containing a protected ester moiety or as an α,β-unsaturated ketone containing a highly functionalized β-carbon atom. This rich functionality, from either perspective,



(1a-c)



(2a-d)



(3a-c)

a; $n = 0$; $R^1 = Me$; $R^2 = H$
b; $n = 1$; $R^1 = Me$; $R^2 = H$
c; $n = 1$; $R^1R^2 = -[CH_2]_4-$
d; $n = 1$; $R^1 = R^2 = H$

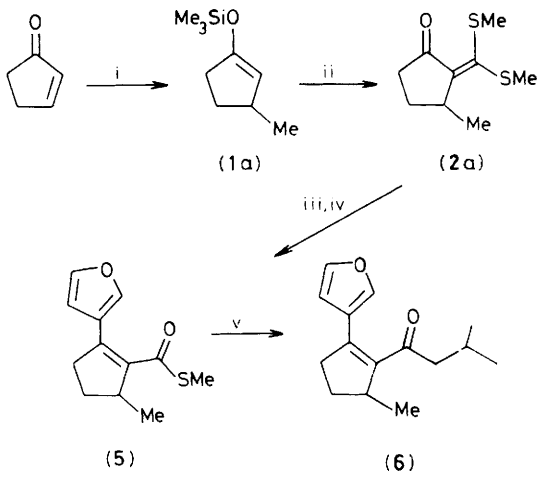
Table 1

Entry	Substrate[a]	Base	Solvent	Temp./°C	% Yield[b] (2)	(3)
1	(1a)	LHMDS	THF[c]	−78 to 0	75	12
2				25	40	27
3		LDA		−78 to 0	40	24
4	(1b)	LHMDS			43	19
5				25	35	32
6		LDA		−78 to 0	52	15
7			Et_2O		45	12
8		Et_2NLi	THF		17	16
9	(1c)	LHMDS			0	22
10				25	0[d]	19

[a] The enolate anion was generated with methyl-lithium. [b] Yields are based upon isolated products purified by medium pressure liquid chromatography on silica gel. The assigned structures were in accord with i.r., ^1H n.m.r., and ^{13}C n.m.r. spectral data. Products gave satisfactory C and H combustion analysis. [c] THF = tetrahydrofuran. [d] Under these conditions (4) was formed in 10% yield.

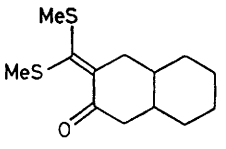
holds considerable potential for the sequential regioselective construction of new carbon–carbon bonds *via* a cascade of 1,2- and/or 1,4-nucleophilic addition reactions.[1,2] The development of conditions for preparing α-oxoketene dithioacetals from kinetically generated enolate anions[3] suggested a synthetic route to the regiospecifically substituted α-oxoketene dithioacetals (**2a**—**c**) involving regiospecific enolates generated by conjugate addition or reduction reactions.

Initial attempts to prepare (**2a**) in a one-pot process resulted in modest yields (40%) which could be significantly improved by utilization of a two-step procedure (Scheme 1). Reaction of cyclopent-2-enone with lithium dimethylcuprate followed by quenching with chlorotrimethylsilane gave the regiospecific silyl enol ether (**1a**) in 88—99% yield. Regeneration of the regiospecific enolate with methyl-lithium[4] followed by sequential addition of carbon disulphide and lithium hexamethyldisilazide generated a dithiolate dianion which afforded (**2a**) in 75% yield upon quenching with methyl iodide. Attempts to extend this procedure to the silyl enol ethers (**1b,c**), however, were only partially successful and it was soon evident that substantial quantities of the bis(ketene dithioacetal) (**3b,c**) were formed. The yields of (**2a,b**) and (**3a**—**c**) were affected by solvent, temperature, and base and substrate structure (Table 1). Substrate (**1a**), for example, afforded higher yields of (**2a**)



(1a) (2a) (5) (6)

Scheme 1. i, Me_2CuLi, Et_2O, −40 to 0 °C; Me_3SiCl, HMPA, Et_3N; ii, MeLi, THF, HMPA, room temp., 1 h; CS_2, −78 to 0 °C; $(Me_3Si)_2NLi$, THF, −78 °C; MeI (3.0 equiv.); iii, 3-lithiofuran, Et_2O, −78 °C; iv, 10% aq. HBF_4, 80:20 THF–H_2O, room temp., 16 h; v, Bu^t_2CuLi, Et_2O, −40 °C.



(4)

with lithium hexamethyldisilazide (LHMDS) than with lithium di-isopropylamide (LDA) while the effect of these bases on the formation of (**2b**) from (**1b**) (compare entries 1 and 3 *vs.* 4 and 6) was reversed. The structures of (**2a,b**) and (**4**) were assigned from their ^1H and ^{13}C n.m.r. spectral data. The ^{13}C n.m.r. spectrum of (**2a**) [$CDCl_3$, δ 37.7 p.p.m., (CH_2)] and (**2b**) [$CDCl_3$, δ 42.3 p.p.m., (CH_2)] displayed a downfield methylene resonance characteristic of the C-5 and C-6 absorptions, respectively, of 3-methylcyclopentanone [$CDCl_3$, δ 46.7 (C-2), 38.5 p.p.m. (C-5)] and 3-methylcyclohexanone [$CDCl_3$, δ 49.9 (C-2), 41.0 p.p.m. (C-6)].[5] Similarly, the downfield absorptions of the methine protons in (**2a**) ($CDCl_3$, δ 3.05—3.44) and (**3a**) ($CDCl_3$, δ 3.00—3.42) and in (**2b**) ($CDCl_3$, δ 3.47—3.81) and (**3b**) ($CDCl_3$, δ 3.22—3.64) provided collaborative confirmation of the ^{13}C n.m.r. structural assignments. Compounds (**3a**) and (**3b**) also displayed clearly distinguishable absorptions between δ 2.41—2.97 and 2.66—2.92, respectively, for the allylic methylene protons. Under similar reaction conditions at 25 °C (entry 10), the silyl enol ether (**1c**) did not afford (**2c**) but gave the regioisomer (**4**) [$CDCl_3$, δ C 48.9 p.p.m. (CH_2); *trans*-bicyclo[4.4.0]decan-3-one,[6] dioxane, δ 48.7 p.p.m. (C-2)] in 10% yield. Clearly, the formation of (**3a**—**c**) and (**4**) involves equilibrium processes that are difficult to control and which are facilitated by alkyl substitution at the γ-carbon atom of (**1a**—**c**). The yields of (**2a**—**c**) decrease along the series (**1a**)—(**1c**) (entries 1, 6, and 10) as this steric hindrance increases. The substrate sensitivity of these carbon disulphide alkylation reactions was surprising in view of the facile preparation of (**2d**) (84%) under similar reaction conditions utilizing LDA as the base.[3] Complex mixtures were also obtained in attempts to prepare the corresponding methyl β-ketodithioesters indicating that the equilibria occur during the initial carbon disulphide alkylation.

The α-oxoketene dithioacetal (**2a**) is a key intermediate in the synthesis of the toxic furanosesquiterpene myodesmone

recently isolated from *Myoporum deserti* and *Myoporum acuminatum*.[7] Nucleophilic addition of 3-lithiofuran to (**2a**) followed by acid promoted rearrangement affords the α,β-unsaturated thioester (**5**) [i.r. (neat) 1653 cm^{-1}(s); ^1H n.m.r. (60 MHz, CCl_4) δ 1.23 (d, *J* 7 Hz, 3H), 1.40—1.97 (m, 1H), 1.97—2.57 (m, 1H), 2.33 (s, 3H), 2.80 (dt, *J* 7, *J* 2 Hz, 2H), 3.08—3.68 (m, 1H), 6.63 (m, 1H), 7.30 (m, 1H), 7.98 (s, 1H)] in 71% yield (Scheme 1). The thioester (**5**) is readily converted into (±)-myodesmone (**6**) [i.r. (neat) 1675 cm^{-1}(s); ^1H n.m.r. (90 MHz, $CDCl_3$) δ 0.90 (d, *J* 6.6 Hz, 6H), 1.13 (d, *J* 6.8 Hz, 3H), 1.34—1.72 (m, 1H), 1.78—2.19 (m, 1H), 2.19—2.47 (m, 3H), 2.70 (tt, *J* 7, *J* 1 Hz, 2H), 3.20 (br. q, *J* 7 Hz, 1H), 6.41 (m, 1H), 7.36 (t, *J* 1.7 Hz, 1H), 7.72 (br. s, 1H)†] in 53% yield upon treatment with lithium di-isobutylcuprate at −40 °C in diethyl ether.[8]

In summary, the preparation and conversion of the regiospecifically substituted α-oxoketene dithioacetal (**2a**) into (±)-myodesmone illustrates the powerful synthetic potential of α-oxoketene dithioacetals for sequential regioselective carbon–carbon bond constructions.

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† The 90 MHz ^1H n.m.r. spectrum of synthetic (±)-myodesmone was virtually identical to a 100 MHz spectrum of the natural material kindly provided by Professor M. D. Sutherland.

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