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SELENO- AND SULPHENO-LACTONISATION REACTIONS OF 5,7-DIENOIC ACIDS

by Michael R. Huckstep and Richard J.K. Taylor*

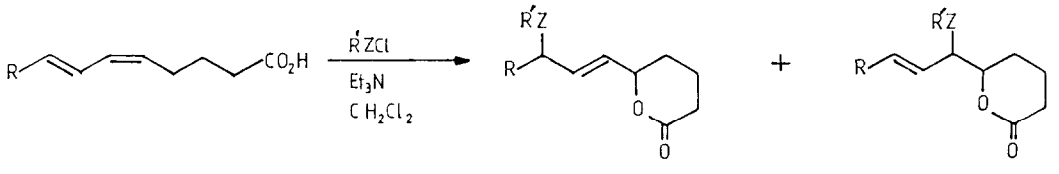
School of Chemical Sciences, University of East Anglia, Norwich, NR4 7TJ

and Michael P.L. Caton
May & Baker Ltd., Dagenham, Essex, RM10 7XS

Summary: The seleno- and sulpheno-lactonisation reactions of 5Z,7-octadienoic acid (1) and 5Z,7E-nonadienoic acid (2) have been studied as a means of preparing functionalised lactones; δ-lactone formation occurs in all cases but whereas octadienoic acid (1) undergoes only 1,4-addition across the diene unit the outcome of the corresponding reactions of nonadienoic acid (2) depends on the choice of the electrophilic reagent employed in the cyclisation reaction. Regioselective 1,4- (conjugate) addition can be obtained with nonadienoic acid (2) providing alkylsulphenyl halides are used in the cyclisation reaction.

The seleno-[1] and sulpheno-[2,3] lactonisations of unsaturated carboxylic acids have been studied extensively but these reactions have not been applied to conjugated dienoic acids until recently. The report by Pearson et al[4] on the seleno-lactonisation of dienoic acids as a means of preparing functionalised γ-lactones prompts us to disclose our own results in this area. We have found that both seleno- and sulpheno-lactonisations can be used to prepare δ-lactones from dienoic acids. More importantly, however, we have established for the first time that the choice of electrophilic reagent can influence the regiochemical outcome of the reaction with respect to the mode of addition (1,2-/1,4-) across the diene unit. The results of our investigation are shown in Scheme 1 and the Table.

SCHEME 1



(1), R=H
(2), R=Me

(3), R=H
(5), R=Me

(4), R=H
(6), R=Me

a, R'Z=PhSe
b, R'Z=PhS
c, R'Z=MeS
d, R'Z=$MeO_2CCH_2CH_2S$

TABLE

Starting Materials	Conditions	Yield	Products[a] [Ratio]
(1) + PhSeCl	-78°C, dark	95%	(3a)
(1) + PhSCl	25°C	82%	(3b)
(2) + PhSeCl	-78°C, dark	91%	(5a):(6a)[b] [1:1]
(2) + PhSCl	-78°C	64%	(5b):(6b)[c] [1:1]
(2) + MeSCl[d]	-78°C	22%	(5c)
(2) + $MeO_2CCH_2CH_2SCl$[e]	-78°C	69%	(5d)

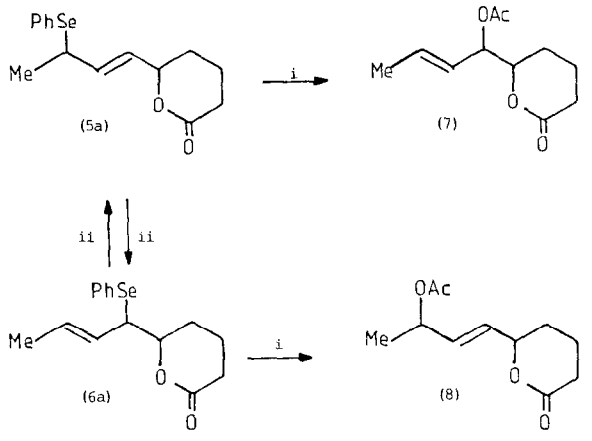
[a] All new compounds are fully characterised.
[b] Isomers could be separated only when light excluded during chromatography.
[c] Isomers could not be separated.
[d] The corresponding sulphenyl bromide gave 24% yield; in both reactions unreacted (2) was also recovered.
[e] At 25°C the yield was 72%.

Treatment of 5Z,7-octadienoic acid (1) with phenylselenyl chloride or phenylsulphenyl chloride gave regioselective δ-lactone formation, and exclusive 1,4- (conjugate) addition to the diene moiety, the products (3) being obtained in good yield. That 1,4-addition had occurred was evident from the ^{1}H-n.m.r. spectra; there are only two vinyl protons and the coupling is consistent with the assigned structure [e.g. for (3a): H-6, dd, J14.4Hz and J5.8Hz; H-7, dt, J14.4Hz and J7.2Hz]. In addition, the n.m.r. spectra demonstrate that the newly formed double bonds have the trans-configuration.

However, on changing the substrate to 5Z,7E-nonadienoic acid (2), regioselectivity with respect to the diene system was lost. Treatment of dienoic acid (2) with phenylselenyl chloride at -78°C in the dark gave a mixture of two γ-lactones (ca. 1:1) which could be separated by preparative centrigual chromatography provided that light was excluded. This procedure gave lactones (5a) and (6a) in approximately equal amounts (91% combined yield).

The two isomers could be readily distinguished by 400 MHz ^{1}H-n.m.r. spectroscopy and double resonance experiments. These spectra also confirmed the trans-configurations of the double bonds [(5a), J16Hz; (6a), J15Hz] and indicated that both isomers were diastereomeric mixtures (each ca. 1:1). Additional structural confirmation was obtained by oxidising the allylic selenides (5a) and (6a), independently, to the corresponding selenoxides which underwent [2,3]-sigmatropic rearrangement in situ to produce allylic alcohols which were acetylated to give the allylic acetates (7) and (8), respectively, uncontaminated by each other (Scheme 2).

SCHEME 2



Reagents (i) H_2O_2 then Ac_2O

(ii) Sunlight, 4-toluenesulphonic acid or heat.

Both allylic selenides (5a) and (6a) underwent facile interconversion (Scheme 2). Dichloromethane solutions of either isomer were converted into a mixture (ca. 1:1) of the two after exposure to sunlight for 1 hour or 4- toluenesulphonic acid for 5 hours. Thermal interconversion took place more slowly on heating the allylic selenides in toluene in the dark (12-18 hours) or on storing as neat liquids (>48 hours). These observations are in accord with a recent report describing the ease with which allylic phenylselenides undergo [1,3]-rearrangements, particularly under photolytic conditions.[5]

Phenylsulphenyl-lactonisation of dienoic acid (2) also gave a mixture of 1,4- and 1,2-adducts (5b) and (6b) (ca. 1:1 by n..m.r.), but although chromatographically distinct, the isomers could not be separated by chromatography even when light was excluded. These difficulties could be due to facile interconversion of isomers (5b) and (6b) by a [1,3]-phenylthio-shift, a well documented process.[6]

It seemed likely that allylic alkylsulphides would be less prone to [1,3]-rearrangements and so alkylsulphenyl halides were employed in the lactonisation reactions. Treatment of dienoic acid (2) with methanesulphenyl chloride produced only the 1,4-adduct (5c) although the yield was low. Changing to methanesulphenyl bromide increased the yield of (5c) only slightly to 24% and again there was no sign of the allylic-isomer (6c). In both of these reactions unreacted starting material (2) was also recovered. All attempts to isomerise the allylic sulphide (5c) into its regioisomer (6c) under thermal, photochemical, or acidic conditions were unsuccessful.

Eventually we found that synthetically useful yields of the 1,4-addition product (5d) were obtained when methyl (3-chlorothio)- or (3-bromothio)propanoate[3] were used for the sulpheno-lactonisation of dienoic acid (2). Compound (5d) was also thermally and photochemically stable. These results indicate that alkylsulphenic acids are the reagents of choice for the conjugate lactonisation process outlined in Scheme 1 if the products are liable to undergo facile [1,3]-rearrangements.

Further studies are underway to gain an insight into the mechanism of these reactions and to apply this new procedure for the preparation of 5-substituted valerolactones in natural product synthesis.

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