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STANNYL ESTER CYCLIZATIONS

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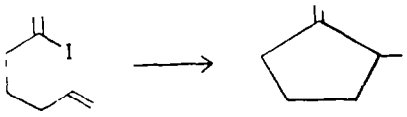
ABSTRACT

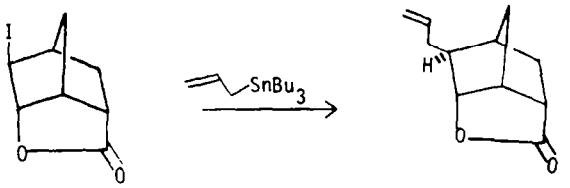
Alpha halo stannyl esters react with alkenes to afford lactones. The reaction is catalyzed by AIBN. The reaction proceeds best with electron rich alkenes. The mechanistic aspects of this novel reaction are discussed. This reaction can also be conducted intramolecularly to produce bicyclic lactones. An approach to the lignan system is presented.

Synthetic applications of free radical chemistry have increased significantly. This undoubtedly reflects the recognition of the unique opportunities which the use of radicals offers the organic chemist. Much of our basic understanding of radical chemistry is due to the pioneering efforts of Julia(1), Beckwith(2) and Barton(3). Excellent reviews and books document this earlier work.(4) Recently, new free radical based methods for carbon-carbon bond formation have been reported. One powerful contribution was the vinyl radical cyclization developed by Stork. An example of this reaction is depicted below. Both five and six membered rings can be prepared. The resulting radical can be intercepted by an isocyanide to form a nitrile.(5)



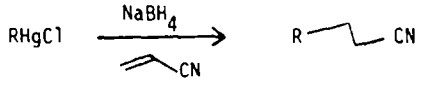
(1)

Keck and coworkers have cleverly employed allyl tin chemistry to append an allyl group to an existing carbon framework by displacement of a halide. This chemistry is also applicable to carbohydrate chemistry.(6)



(2)

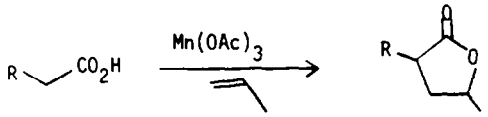
Giese and collaborators have developed a novel and extremely useful reaction of organomercurials with unsaturated carbonyl compounds.(7) This chemistry further increases the synthetic utility of the oxymercuration and aminomercuration reactions. (8) Giese's reaction has been used synthetically by both Danishefsky(9) and Kozikowski(10). The basic reaction is illustrated by the following example:



(3)

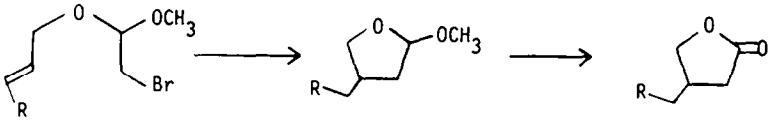
Total syntheses using radical based methodology have been reported by Hart(11), Baldwin(12) and Kozikowski(13).

The formation of lactones by a radical process was first described by Heiba and Dessau(14). They treated acids with manganic triacetate in the presence of alkenes and obtained good yields of lactones.



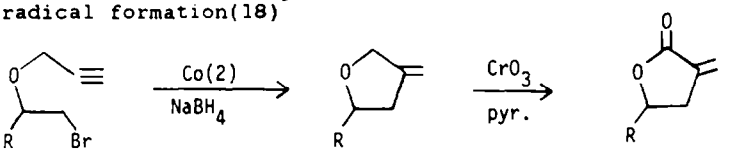
(4)

Recently, both Fristad(15) and Corey(16) have published important extensions of this basic reaction. Stork and coworkers have disclosed the interesting reaction sequence illustrated below for the formation of lactones(17).



(5)

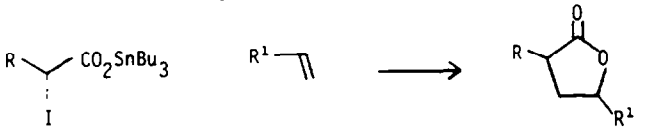
Tada has also devised a clever synthesis of lactones using cobalt complexes to promote radical formation(18)



(6)

Other radical based lactone formations have been reported by Burke(19) and by Clive(20).

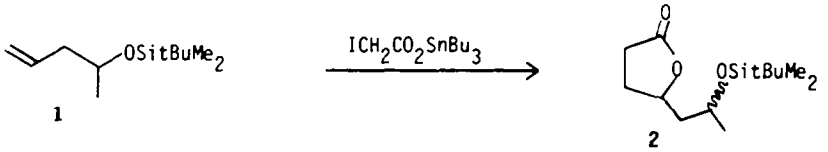
In connection with our interest in radical cyclizations, we investigated the reaction depicted below.(21)



(7)

As shown in Table 1, many alkenes afford good to excellent yields of lactones. Functional groups such as acetals, alcohols and carbonyl groups are stable to the reaction conditions. Most of the examples which are unsuccessful involve either sterically hindered alkenes or alkenes bearing an electron withdrawing group. The latter case is consistent with the reaction profile of an electron deficient radical. In the case of acyclic enol ethers, the initially formed lactone rearranges to an ester aldehyde. This is a thermal process. The different behavior of cyclic versus acyclic enol ethers probably has its origins in the stereoelectronic effect. Deslongchamps, in his classic work on acetal openings, has observed similar effects.(22)

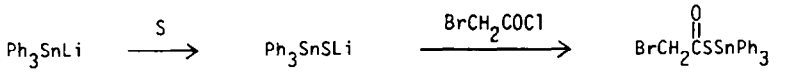
The radical cyclization reaction creates a new stereogenic center. Accordingly, the following experiments were conducted to determine whether an allylic or homoallylic stereogenic center affected the stereochemical course of the lactone forming reaction. Silyl ether 1 was chosen, since lactone 2 had already been prepared independently and detailed NMR data was available. Analysis of the purified product by 300 MHz NMR showed that essentially equal amounts



(8)

of the two diastereomers had been formed. Analogous results were obtained using the tert-butyldimethylsilyl ether of 3-buten-2-ol.

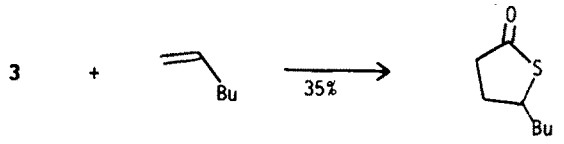
The question whether other heterocyclic rings could be formed was next adressed. A few simple stannylthioesters had already been prepared. The stannyl ester of 2-bromothioacetic acid was synthesized as depicted below.



(9)

The lithium salt of triphenyltin thiol was a stable solid. It was treated with an excess of bromoacetyl chloride to afford 3. The stannyl thioesters which were prepared
were extremely hygroscopic. When reacted with representative alkenes, they afforded the desired thiolactones, albeit in only modest yields. We were able to prepare the corresponding N-stannyl bromoamide from iodoacetamide.

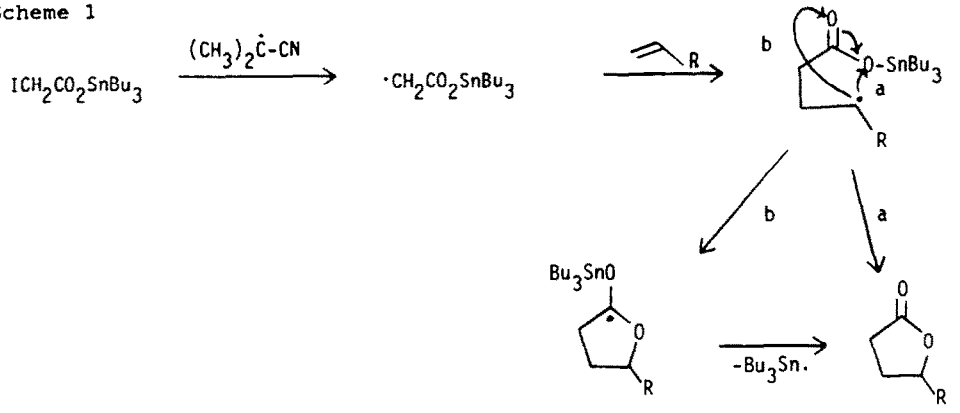
However, its reaction with 1-hexene did not afford a lactam.



(10)

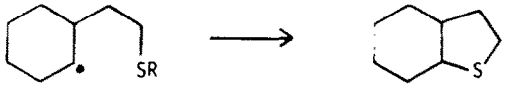
The possibilities which seem most reasonable for the mechanism of this novel lactone forming reaction are illustrated below. The initially described one, depicted in path A, involves an SHi type reaction on the oxygen atom of the stannyl ester.

Scheme 1



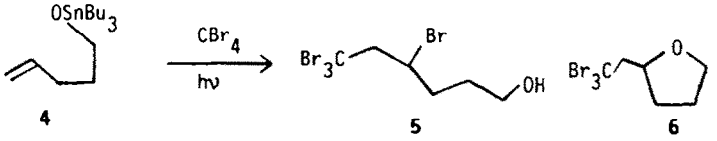
An alternative mechanism shown in path B requires a radical attack on the carbonyl oxygen atom. This leads to an acetal type radical which fragments to form the lactone and the tributylstannyl radical which continues the radical chain.

The formation of thiolactones would at first seem to rule out anything except the SHi mechanism. However, Kampmeier and coworkers have reported the interesting reaction shown below.(23) The reaction may proceed by an SHi type process on sulfur. However, the intermediacy of a sulfuranyl radical which later fragments is a distinct possibility.



(11)

Interestingly, direct radical displacements at saturated aliphatic carbon atoms are rare. This is in dramatic contrast to the situation in carbanion chemistry. The only example was reported recently by Jackson and Townson who proposed the SH2 reaction of trifluoromethyl radical with neopentane.(24) No radical displacements on oxygen atoms have been documented. In order to design a situation in which this could occur, stannyl ether 4 was synthesized and was reacted with carbon tetrabromide under conditions which

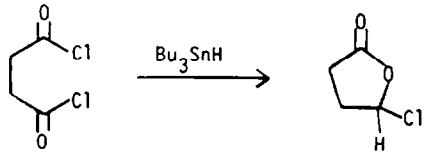


4 5 6

(12)

generate the tribromomethyl radical. Compound 5 was isolated in 60% yield. The product of an SHi reaction on the stannyl ether could not be found. In this experiment the electronic environment around the oxygen atom is somewhat different. However, the result does render path A less convincing. Path B involves an attack on the carbonyl oxygen atom. Using Baldwin's terminology this is a 5-endo trig process.(25) In a series of elegant papers, Baldwin has demonstrated that such processes are disfavored.(26) Other researchers have substantiated this result. On the other hand,

Kuivila and coworkers have reported the interesting transformation depicted below. It is possible that this reaction proceeds by a 5-endo trig type process.(27)

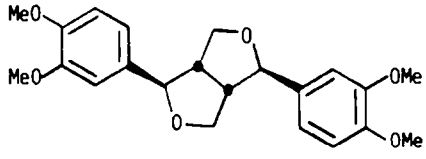


(13)

The intramolecular reaction of a bromostannyl ester with an alkene was next examined. Originally, we had intended to deprotonate and then alkylate the tributylstannyl ester of bromoacetic acid. However, the anion proved to be extremely unstable. Even the reaction with benzaldehyde generated several products. The reaction sequence depicted below was

(14)

successful. It involved the halogenation of readily available 6-heptenoic acid(28) followed by formation of the stannyl ester using bistributyltin oxide. The resulting stannyl ester was heated in boiling benzene with 5 mole percent of AIBN for four hours. The major product(40%) was the desired bicyclic lactone as evidenced by the disappearance of the olefinic absorptions in the NMR and by the emergence of an absorption at 1760 in the infrared spectrum. Having defined the feasibility of an intramolecular cyclization, extension of this concept to natural products synthesis became the next priority. The first targets chosen were a subset of the lignans.(29)



(15)

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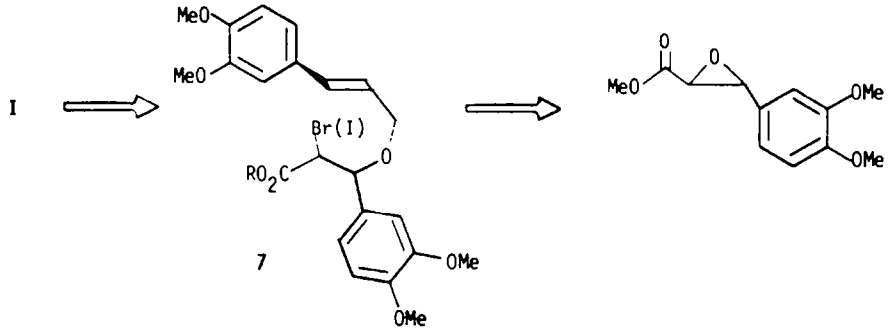
Although a number of good syntheses already exist, our approach is conceptually quite different. Moreover, it illustrates some unique features that synthesis via radical intermediates makes possible. The retrosynthetic plan is shown below.

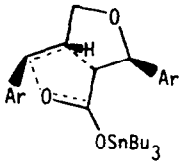
Scheme 2



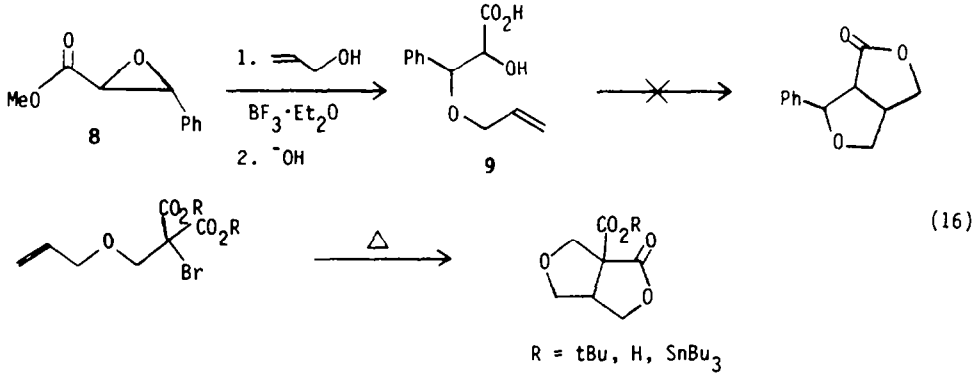
Note that the key step involves the formation of a radical with a beta alkoxyl group. This would not be possible using carbanion chemistry, because elimination to an alkoxide anion would result. The natural product contains four stereogenic carbon atoms. Two of them will be set relative to each other because a cis-bicyclo[3.3.0]octane is thermodynamically much more stable than its trans counterpart. Since bicyclo[3.3.0] octanes exist in a highly folded conformation, it was anticipated that both the initial stereogenic center(in 7) which could direct the ensuing stereochemistry and

the last-formed center would be oriented such that the aromatic ring was on the exo face of the molecule.

Scheme 3



In practice, a model system was first constructed. The Lewis acid catalyzed addition to epoxyester 8(30) followed by ester hydrolysis produced 9. This hydroxyacid could be converted into the tributylstannyl ester. However, the hydroxyl group could not be transformed into a bromide or iodide without decomposition. This problem was circumvented as shown below. Heating the ester afforded a 50% yield of the desired bicyclic lactone.

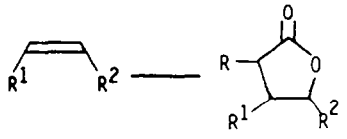


(16)

R = tBu, H, $SnBu_3$

Extension of these results to the lignan system should readily be possible and is now in progress.

In summary, stannyl ester cyclizations represent a viable alternative to carbanion or hydride based methods. The compatibility of unprotected hydroxyl groups plus the lack of problems relating to beta elimination combine to make this method a versatile one. Additionally, the reaction can also be employed intramolecularly to produce novel bicyclic products.

Table I. $XCHRCO_2SnBu_3$ +  ——

Entry	X	R	R'	R^2	% yield[a]
1	I	H	H	Bu	76
2	Br	H	H	Bu	70
3	I	H	$-CH_2CH_2O-$		78
4	I	H	H	Am	75
6	I	H	H	Oct	76
7	I	H	H	CH_2SiMe_3	56
8	I	H	$(CH_2)_4$		-
9	I	H	H	OEt	36[b]
10	I	CH_3	$-CH_2CH_2O-$		72[c]
11	I	CH_3	H	Bu	75[c]
12	I	H	Ph	CO_2Et	-
13	I	H	H	CH_2OH	73
14	I	H	H	$-C(CH_3)=CH_2$	-

a. Yield after chromatography
b. An equal amount of aldehyde ester was formed.
c. The lactones are approximately a 50:50 mixture of diastereomers.

EXPERIMENTAL SECTION

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Dichloromethane was distilled from phosphorus pentoxide. Infrared spectra were determined on a Beckman IR-4250 spectrometer. Nuclear magnetic resonance spectra were determined on a Varian EM 360 60 MHz instrument and on a Nicolet 300 MHz instrument. Carbon-13 NMR spectra were determined on a JOEL FX-90Q Fourier transform instrument. Elemental analyses were performed by Galbraith laboratories, Inc.

General Procedure for the Formation of Stannyl Esters.
Two equivalents of the requisite acid and one equivalent of bistributyltin oxide were heated to 130 C for 30 min. The mixture was allowed to cool and was then extracted with hot hexanes. The hexanes were removed in vacuo to afford the stannyl ester. The stannyl esters were sufficiently pure for subsequent reactions.

Tributylstannyl iodoacetate:NMR(CDCl3) 0.85-1.90(m, 27H), 3.70(s, 2H). IR(nujol) 1385,1576, 1598. Mass spectrum,
m/e calcd for C10H20SnO2I(M+ - Bu) 418.95301, found 418.95281.

General Procedure for the Formation of Lactones. One equivalent of the halo ester, three equivalents of the alkene and 5 mole percent of AIBN were refluxed in benzene(1 M) for 8 h. After partition between acetonitrile and hexanes, the crude product was isolated from the acetonitrile layer. It was chromatographed on silica gel to afford the pure product.

4-Octyl butyrolactone. NMR(CDCl3) 0.82-2.83(m, 21H), 4.25-4.61(m,1H). IR(film) 905, 1175, 1775. Anal calcd for C12H2202: C,72.68;H,11.18. Found: C,72.61;H,11.28.

Hexahydro furo 2,3-b furan-2-one. NMR(CDCl3) 1.45-3.45(m, 5H), 3.72-4.22(m, 2H), 6.07(d,J=5 Hz, 1H). IR(film) 732, 970, 1783. Mass spectrum, m/e calcd for C6H7O3(M+ - H) 127.03952, measured 127.03952. Anal calcd for C6H8O3: C, 56.25; H, 6.29. Found: C, 56.03; H, 6.34.

4-Butyl butyrolactone. NMR(CDCl3) 0.70-2.85(m, 13H), 4.25-4.72(m, 1H). IR(film) 1010, 1175, 1462, 1770.

4-Hydroxymethyl butyrolactone. NMR(CDCl3) 1.85-2.75(m, 4H), 3.32-3.82(m, 3H), 4.36-4.80(m, 1H). IR(film) 1175, 1345, 1760, 3420. Mass spectrum M+ 116.

4-Trimethylsilylmethyl butyrolactone. NMR(CDCl3) 0.10(s, 9H), 0.95-2.65(m, 6H), 4.30-4.78(m, 1H). IR(film) 830, 865, 1168, 1250, 1775. Mass spectrum, m/e calcd for C7H13O2Si(M+ - Me) 157.06848, measured 157.06802. Anal calcd for C8H16O2Si: C, 55.79;H, 9.30. Found: C, 55.58; H, 9.26.

3-Oxabicyclo 3.3.0 octan-2-one. 300 MHz NMR(CDCl3) 1.52-2.20(m, 7H), 2.85-3.15(m, 1H), 3.92-4.10(m, 1H), 4.47-4.56 (m, 1H). IR(flim) 1760, 1175. C-13 NMR(CDCl3): 25.44, 30.62, 33.69, 38.94, 44.23, 73.47, 180.87. Mass spectrum m/e: 67, 81, 126. High resolution mass spectrum for C7H10O2 requires m/e 126.06808, found 126.0684.

Triphenylstannyl bromoacetate 3. The triphenylstannylthio lithium was prepared according to the literature(31).
It was reported to be a dimer. The tin dimer(0.39 g,0.5 mmol) in 3 ml THF was slowly added to bromoacetyl chloride(0.16 ml, 2.0 mmol) in 3 ml THF at 78 C. The reaction was stirred at -78 C for one h and then at room temperature for 4 h. The solution was diluted with toluene, filtered through Celite and then concentrated in vacuo. The product was unstable to air and was sufficiently pure for the thiolactone forming reaction.

3: NMR(CDCl3) 3.95(s, .8H), 4.20(s, 1.2H), 7.32-8.00(m, 15H).

Tributyl(4-pentenyloxy)stannane 4. Tributylethoxystannane(2.20 g, 10 mmol) and 4-penten-1-ol(1.03 ml, 10 mmol) were heated to 120 C in a Kugelrohr for 3 h. After the ethanol had distilled from the bulb, 1.85g(60% yield) of product was isolated.

4: MNR(CDCl3) 0.80-1.80(m, 29H), 1.85-2.42(m, 2H), 3.68(t, J= 6 Hz, 2H), 4.75-6.20(m, 3H). IR(film) 1450, 990, 910.

Reaction of 4 with carbon tetrabromide. A degassed solution of ether 4(0.35 g, 0.93 mmol) and carbon tetrabromide(0.31 g, 0.93 mmol) in 2 ml of carbon tetrachloride was irradiated with a sun lamp for 8 h. After partitioning the resulting solution between acetonitrile and hexanes, The acetonitrile layer was concentrated in vacuo to afford 0.69 g of crude product. No absorptions corresponding to 6 were apparent. Only the adduct was obtained.

5: NMR(CDCl3) 1.32-2.30(m, 4H), 2.60-2.90(m, 2H), 3.40-3.85(m, 3H). IR(film) 720, 898, 3450. No parent ion could be found in the mass spectrum.

2-Iodo-6-heptenoic acid. The dianion was prepared by the method of Pfeffer and Silbert(32). The yield was 57%.

Methyl 3-allyloxy-2-hydroxy-3-phenylpropionate 8. To a solution of 2-phenyl-oxiranecarboxylic acid methyl ester(3.79 g, 21.3 mmol) in 21.5 ml of allyl alcohol at 0 C was added boron trifluoride etherate(0.52 ml). The solution was stirred at 0 C for 15 min and then at room temperature for 2 h. It was diluted with ether, washed with sodium bicarbonate, dried and concentrated to afford the product. After purification, 4.0 g(79.6%) of 8 was isolated.

8: This was an 8:1 mixture of diastereomers as evidenced by 300 MHz NMR. Only the major diastereomer peaks are reported. 300 MHz NMR(CDCl3) 3.70(s, 3H), 3.78-3.90(m, 1H), 4.01-4.10(m, 1H), 4.50(bs, 1H), 5.16-5.30(m, 2H), 5.80-5.95(m, 1H), 7.28-7.42(m, 5H). IR(film) 1085, 1450, 1745. Mass spectrum, m/e calcd for C10H10O3(M+ - C3H6O) 178.06300. measured 178.06320.

3-Allyloxy-2-hydroxy-3-phenylpropionic acid 9. Ester 8(1.89 g, 8.0 mmol) was dissolved in 8 ml methanol. Potassium hydroxide(0.46 g, 8.2 mmol) in 8 ml water was then added to the ice cooled solution. The solution was stirred at room temperature for 3 h, diluted with water and ether and separated. The ether layer was extracted three times with sodium bicarbonate. The aqueous layers were combined and acidified to pH 3. The ether extracts from the acidified aqueous solution were dried and concentrated to produce 1.43 grams(80.4%) of a white solid.

9: MNR(CDCl3) 3.80-4.05(m, 1H), 4.35-4.80(m, 2H).4.95-6.25(m,3H), 7.36(s, 5H). IR(film) 1725, 3400(broad). Mass spectrum m/e 222.

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