

The Stereoselective Synthesis of Unsaturated Nine-membered Lactones using the Malherbe–Bellus Variant of the Claisen Rearrangement

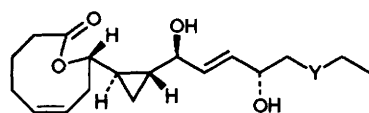
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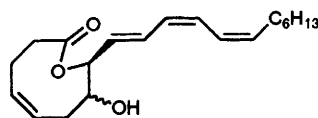
The title reaction has been used to prepare nine-membered lactones commencing from 2-vinyltetrahydrofurans and dichloroketene; the resulting Δ^5 -dichlorolactones are exclusively *trans* but dechlorination using Bu_3SnH –AIBN (azoisobutyronitrile) achieves concomitant isomerisation to give the *cis*-unsaturated lactones.

The discovery of the bioactive marine metabolites halicholactone **1**,¹ neohalicholactone **2**¹ and the ascidiatrienolides (e.g. ascidiatrienolides A and B, **3**)^{2‡} has stimulated a great deal of recent interest in the development of synthetic routes to unsaturated nine-membered lactones. The proposed structures also attracted our attention with respect to our programme concerned with the synthesis of polyunsaturated natural products,³ particularly those of marine and eicosapolyenoate origin.⁴

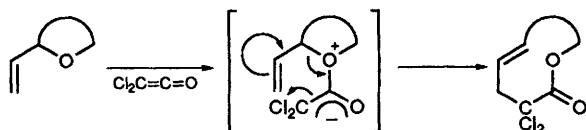
In order to embark on total syntheses of these types of natural products we required an efficient procedure for the construction of the unsaturated lactone moiety. Hydroxy acid lactonisation approaches were an obvious possibility⁵ but even



1; Y = CH_2CH_2
2; Y = $\text{CH}=\text{CH}$



3
Ascidiatrienolide A = α -OH
Ascidiatrienolide B = β -OH



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‡ Note added in proof: the original assignment of the ascidiatrienolides as nine-membered lactones has recently been questioned, and it has been established unambiguously that ascidiatrienolide A is a ten-membered lactone (M. S. Congreve, A. B. Holmes, A. B. Hughes and M. G. Looney, *J. Am. Chem. Soc.*, 1993, **115**, 5815).

with the assistance of a *cis*-alkene⁶ we were concerned about the efficiency of such a procedure (see later). Approaches based on the Claisen rearrangement of vinyl ketene acetals,⁷ as developed by Petrzilka and Holmes *et al.*, were attractive but we decided to investigate the utility of the Malherbe–Bellus variant of the Claisen rearrangement in which allyl ethers are treated with dichloroketene.⁸

In the original study, this chemistry was applied to acyclic systems and to the conversion of 2-vinyltetrahydrofurans into chlorinated ten-membered lactones.⁸ We now report: (i) that this chemistry is extremely useful for the preparation of nine-membered unsaturated lactones from 2-vinyltetrahydrofurans and dichloroketene, (ii) that the methodology is compatible with a silyl ether substituent, (iii) that the product alkenes can undergo a further reaction with dichloroketene to produce novel cyclobutanones, and (iv) that dechlorination of the Claisen products using Bu_3SnH –AIBN achieves concomitant isomerisation to give *cis*-unsaturated lactones.

In order to establish the viability of this procedure for preparing nine-membered lactones, the readily available^{9§} 2-vinylfuran **4a** was treated with CCl_3COCl /activated zinc¹⁰ in a range of solvents (see Scheme 1 and Table 1). Hexane and tetrahydrofuran (THF) were found to be unsuitable but lactone **5a**¶ was formed in diethyl ether,⁸ dibutyl ether, diethyl ether–hexane and toluene as shown in Scheme 1. Diethyl ether–hexane was the preferred solvent, lactone **5a** being obtained in 65% yield. In toluene as solvent, the expected product was accompanied by a significant amount of byproducts (**7**, 18%; *o:p*, ca. 3:2), presumably resulting from the electrophilic substitution of toluene by the acylated derivative of **4a**. In addition, examination of the crude product mixtures by IR spectroscopy indicated the likely presence of cyclobutanone byproducts (1810 cm^{-1}) but they did not survive silica gel chromatography.

This procedure was next applied to the substituted analogues (**4b–e**) with lactones (**5b–e**) being isolated in good yield.

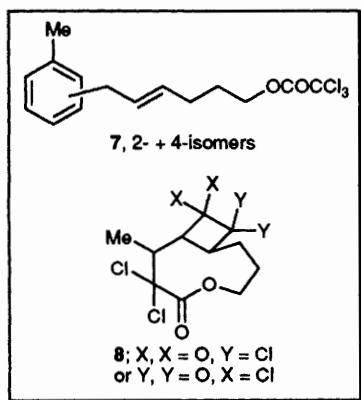
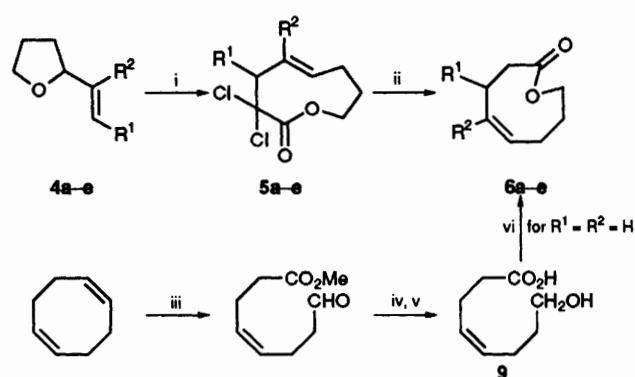
§ Compound **4c** was obtained from tetrahydrofurfural *via* Wittig methodology which will be reported in the full paper.

¶ All new compounds gave consistent spectral and analytical/mass spectrometric data

Table 1 Ring expansion reactions (4 → 5)

Starting material 4	Solvent	T/°C (t/h)	Products, yield (%)
(a)	Diethyl ether	35 (0.5)	5a, 38
(a)	Diethyl ether	35 (4)	5a, 55
(a)	Diethyl ether ^a	35 (20)	5a, 42
(a)	Diethyl ether-hexane	50 (4)	5a, 65
(a)	Toluene	50 (4)	5a, 28
			7, 18
(b)	Diethyl ether-hexane ^b	50 (4)	5b, 60
(c)	Diethyl ether-hexane	50 (3)	5c, 55
(d)	Diethyl ether-hexane	50 (4)	5d, 55
(e)	Diethyl ether-hexane	50 (4)	5e, 64

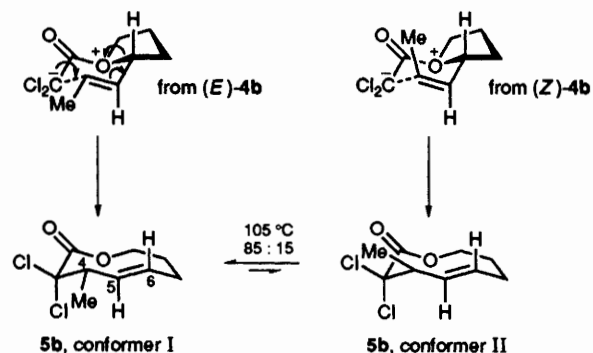
^a Use of Bu₂O as solvent gave a 47% yield after 4 h at 50 °C but higher temperatures gave much lower yields. ^b Use of an excess of CCl₃COCl/Zn gave adduct 8 in ca. 65% yield.



- a; R¹ = R² = H
 b; R¹ = Me, R² = H
 c; R¹ = (*E*)-CH₂OSiPh₂Bu^t, R² = H
 d; R¹ = H, R² = Me
 e; R¹ = H, R² = Me₃Si

Scheme 1 Reagents and conditions: i, Cl₃CCOCl/Zn (see Table 1); ii, Bu₃SnH, AIBN (cat.), PhH, reflux, (a, 66%; b, 73%; c, 75%; d, 70%; e, 77%); iii, O₃, NaHCO₃, CH₂Cl₂-MeOH then Ac₂O, Et₃N (58%); iv, NaBH₄, MeOH (72%); v, LiOH, MeOH (aq), THF (88%); vi, 2-chloro-*N*-methylpyridinium iodide, MeCN, reflux, 32 h (27%). All compounds are racemic.

The compatibility of the *tert*-butyldiphenylsilyloxy substituent with this methodology is noteworthy, and of potential utility in natural product synthesis. In all of these ring expansions (*E*)-alkenes were produced, as expected,⁸ as evidenced by high-field ¹H NMR spectroscopy [e.g. for 5c, H-5, δ 5.43, dd, *J* 16.2, 9.8 Hz]. When an excess of CCl₃COCl/Zn was employed



Scheme 2 All compounds are racemic: for clarity, conformers I and II are shown in enantiomeric forms

for the ring expansion of 4b, lactone 5b was trapped *in situ* to give a single cyclobutanone 8; the regiochemistry of this addition reaction has yet to be established.

The conformational properties of lactone 5b proved to be interesting (Scheme 2). Two conformers were observed by ¹H NMR spectroscopy at room temperature (conformer I: *J*_{5,6} 16.2 Hz; conformer II: *J*_{5,6} 16.8 Hz). The original alkene 4b was a mixture of *trans*- and *cis*-isomers (*E*:*Z* = 77:23) and this ratio was reflected in the product mixture (conformer I: conformer II = 77:23). Samples of 4b with differing isomeric ratios were therefore prepared (*E*:*Z* = 50:50 and 15:85) and again these ratios were reflected in the product conformer mixture. We therefore believe that cyclisation occurs as shown in Scheme 2, with (*E*)-4b producing conformer I and (*Z*)-4b producing conformer II, with the energy barrier for the interconversion of the conformers being sufficiently high for the process to be negligible at *T* ≤ 50 °C. However, using variable-temperature ¹H NMR spectroscopy, it was shown that a mixture in which conformer II predominated (I:II, 15:85) is converted into an equilibrium mixture rich in conformer I (I:II, 85:15) on heating in [²H₈]toluene at 105 °C. Related ten-membered lactones also exist as two major conformers, although rapid interconversion occurs at room temperature.⁸

Tin hydride-mediated dechlorination^{||} was effected next, and high-field ¹H NMR spectroscopy indicated that the products were exclusively the (*Z*)-isomers (*J* ca. 11 Hz).** Apparently *trans*-*cis* isomerisation occurs under radical conditions to produce the (*Z*)-alkene, which is thermodynamically preferred in nine-membered rings.¹¹ In order to confirm this result, Mukaiyama cyclisation¹² were employed to prepare lactone 6a from the stereodefined (*Z*)-alkene 9, readily available from cycloocta-1,5-diene¹³ using the procedure shown in Scheme 1. The two samples of lactone 6a were identical according to ¹H and ¹³C NMR and IR spectroscopy and by chromatographic comparison.

Currently, we are exploring further the scope and limitations of this route to nine-membered lactones, as well as investigating its synthetic utility for the preparation of naturally occurring lactones. This methodology may also prove useful for the preparation of related nine-membered ethers such as obtusenyne.^{7b}

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^{||} Dechlorination of 5a using Zn/AcOH gave a monochloride in 71% yield.

** *Trans*-*cis* isomerisation could be effected without dechlorination by treatment of lactones 5 with PhSSPh-AIBN [(*Z*)-5a, 75%] or PhSO₂H [(*Z*)-5e, 94%].

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