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Dichloroketene reacts, via a [3,3]-sigmatropic rearrangement, with camphor-derived 1,3-oxathianes of α , β -unsaturated aldehydes to give macrocyclic thiolactones in high yield and with complete transfer of chirality. The rearrangement is stereospecific.

The controlled construction of tertiary and quaternary stereogenic centres remains a major challenge in organic synthesis.¹ Methods that achieve this goal are therefore important, but those that also incorporate versatile functionalities suitable for further manipulation proximal to the newly created centre are espe-cially useful. We believed that this ambitious goal could be achieved through a highly ordered ketene [3,3]-sigmatropic rearrangement (Fig. 1). This class of reaction, which is a variant of the Claisen rearrangement, was first described by Malherbe and Belluš² in 1978. In this original work, the [3,3]-sigmatropic rearrangement of intermediate betaines formed from reaction of allyl ethers/thioethers/selenides with dichloroketene was described. Subsequently, it was demonstrated that tertiary allylic amines participate in analogous rearrangements.³ Recently, MacMillan et al.4 have ingeniously applied this reaction to problems of stereocontrol through rearrangement of unsaturated amines mediated by chiral Lewis acids.

Our proposal involved the reaction of dichloroketene with thioacetal $\mathbf{1}$ (Fig. 1). Dichloroketene was expected to attack the more nucleophilic sulfur atom of the thioacetal with complete chemoselection⁵ to give betaine 2. This intermediate should undergo a [3,3]-sigmatropic rearrangement to give the ring expanded thioester 3 stereoselectively.

To achieve high selectivity, it was essential that (i) we started with a single diastereoisomer and enantiomer of the thioacetal, (ii) the thioacetal be incorporated into a conformationally locked ring to avoid erosion of selectivity in the [3,3] rearrangement through ring inversion and (iii) a single diastereoisomer of the intermediate betaine be formed.

Based on these criteria, we targeted the camphor derived thioacetals 5 (Scheme 1) as potential substrates to deliver our goals as, in addition to the features required to achieve stereocontrol, the thioacetal is readily available in both enantiomeric forms. Thus, oxathianes 5a-f were synthesized by



† Electronic supplementary information (ESI) available: experimental data. See http://www.rsc.org/suppdata/cc/b2/b206857e/



Table 1 Synthesis of camphor oxathianes 5

Entry	R	\mathbb{R}^1	5	<i>t</i> /h	Yield 5 ^{<i>a</i>} (%)
1 2	Ph Me	H H	5a 5b	16 16	98 ^b 92 ^b
3	Me	Н	5c	48	51 ^c
4	Ph	Me	5d	16	99 ^b
5	Me	Me	5e	16	78 ^d
6	p-NO ₂ C ₆ H ₄	Н	5f	16	88 ^b

 a Isolated yield after silica gel chromatography (light petroleum, bp 40–60 °C). b Recrystallization from pentane at -20 °C. c Recrystallization from absolute ethanol at -78 °C. d **5e** was obtained as an inseparable diastereisomeric mixture of E/Z (84/16 ratio).

condensation of the known hydroxythiol 4 (obtained by LAH reduction of camphor sulfonyl chloride⁶) with unsaturated aldehydes⁷ (Scheme 1, Table 1). As reported,⁷ the starting E/Zratio of enals was maintained in the product and the thioacetal was obtained as a single equatorial isomer. A single recrystallisation was generally required to remove traces of the Zisomers that were present in entries 1-4 and 6.

The key rearrangement was tested on substrate 5a (Scheme 2). We initially employed the reductive protocol⁸ for the *in situ* generation of dichloroketene. Thus, trichloroacetyl chloride was slowly added to a diethyl ether solution of 5a and activated



 Table 2 Signatropic rearrangements of 5a under reductive conditions

Entry	<i>T</i> /°C	t/h	Additive	Yield Yield 7a ^{<i>a</i>} (%) 9a ^{<i>a</i>} (%	
1	r.t.	3		_	37
2	-78	2	_		21
3	0	1	_	_	32
4	r.t.	4	POCl ₃	_	40
5	r.t.	1	DME	48	8
a Isolate	d yield afte	er silica ge	el chromatograp	hy (light pet	roleum).

zinc. However, rather than obtaining the product derived from a [3,3]-sigmatropic rearrangement 7a, 9a was isolated instead, a product formally derived from a [1,3] rearrangement. Indeed, under a number of conditions, 9a was the main product with little or none of the required product 7a (Table 2, entries 1–3). The main by-product in the reactions was hydroxythiol **4** which was presumably formed through ZnCl₂ mediated hydrolysis. POCl₃ has been previously employed to neutralise the Lewis acidity of the reaction mixture in related cyclobutanone formation from unreactive olefins with excellent results.9 However, in this case, 9a was still the major product (entry 4). Finally, using a bidentate ligand,⁹ DME (2 eq.), to sequester $ZnCl_2$, the cycloenlarged product **7a** derived from the [3,3]-sigmatropic rearrangement was obtained in moderate yield, together with a small amount of 9a. Gratifyingly, 7a was formed as a single diastereoisomer, whose relative stereochemistry was determined by NOE (see ESI[†]). Furthermore, exclusive reaction occurred at the sulfur atom to furnish the ten-membered ring thiolactone 7a. The formation of the two products 7a and 9a as single diastereoisomers can be rationalised by considering the structure of the intermediate betaine. Attack at the equatorial lone pair at sulfur (treating related compounds with m-CPBA provides only the equatorial sulfoxide⁶) gives betaine 6(Scheme 2) which, in the absence of naked ZnCl₂, rapidly rearranges via a chair transition state to give 7a. As a single diastereomer of the betaine is formed and because the thioacetal cannot invert, only a single isomer is possible, i.e. the rearrangement is stereospecific.

Formation of 9a is more difficult to rationalise and presumably arises from stabilisation of the enolate by $ZnCl_2$. This slows down the rate of the [3,3]-sigmatropic rearrangement and presumably allows time for the thioacetal to ring open and form the oxonium ion 8 (Scheme 2). Subsequent reaction of the zinc enolate with the oxonium ion 8 then furnishes 9a.



Table 3 Ketene Claisen rearrangement of 5 under elimination conditions

Entry	R	\mathbb{R}^1	5	<i>t/</i> h	Yield 7 (%)
1	Ph	Н	5a	1.8	95 ^{ab}
2	Me	Н	5b	1.5	67 <i>a</i>
3	Me	Н	5c	1	70^{a}
4	Ph	Me	5d	2.5	96 ^b
5	Me Me	Me	5e	1	76 ^{<i>b</i>}
6	p-NO ₂ -C ₆ H ₄	Н	5f	1.5	91 ^b

^{*a*} Isolated yield after recrystallization of the crude reaction mixture from pentane/absolute ethanol at -20 °C. ^{*b*} Isolated yield after silica gel (pretreated with 1% of Et₃N) chromatography (Et₂O/light petroleum, 2/98).

We clearly observed a beneficial effect in yield of 7a from reducing the Lewis acidity of the medium and so sought to improve this further. Thus, dichloroketene was generated in situ by the alternative procedure that employs Et₃N with dichloroacetyl chloride (elimination conditions⁸). When this procedure was applied to 5a, we were delighted to find a very clean conversion to the ketene Claisen product 7a. None of the [1,3] rearranged product was observed with this new protocol. This procedure was applied to the other substrates (Scheme 3, Table 3, entries 2–4 and 6) and in each case single products were obtained in high yield and as single diastereoisomers. Rearrangement of 5d (entry 4) gave 7d bearing a quaternary centre as a single diastereoisomer. In the case of **5e**, the 84/16 ratio of E/Z isomers rearranged to an inseparable 84/16 ratio of diastereoisomers of 7e, thus demonstrating that the rearrangement was stereospecific.

Interestingly, the *E* double bond of **7d** isomerised to the *Z* isomer during silica gel chromatography.¹⁰ Isomerisations of *E* to *Z* double bonds has been previously reported in ninemembered ring lactones¹¹ and indeed it has been shown that the *Z* isomer is thermodynamically more stable than the *E* isomer in nine-membered carbocycles.¹² In order to evaluate the stability of the *E*/*Z* isomers of our ten-membered ring thiolactone **7d**, a Monte Carlo conformational search was conducted (Macro Model V6.5¹³) and indeed the *Z* isomer was found to be 2.5 kcal/mol more stable than the corresponding *E* isomer.

In summary, we have reported the first examples of the ketene Claisen rearrangement of 1,3-oxathianes. Under elimination conditions for the *in situ* generation of dichloroketene, a clean and smooth transformation of easily accessible camphorderived oxathianes of α,β -unsaturated aldehydes occurred to give diastereomerically and enantiomerically pure thiolactones. In addition to achieving the stereocontrolled construction of tertiary and quaternary stereogenic centres, the current process also converts readily available six-membered rings into the much more difficultly accessible ten-membered rings. The process could therefore have applications beyond our original goals.

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