Diastereoselective [2 + 2] Cycloaddition of Dichloroketene with α-Oxyaldehydes and α-Amino Aldehydes

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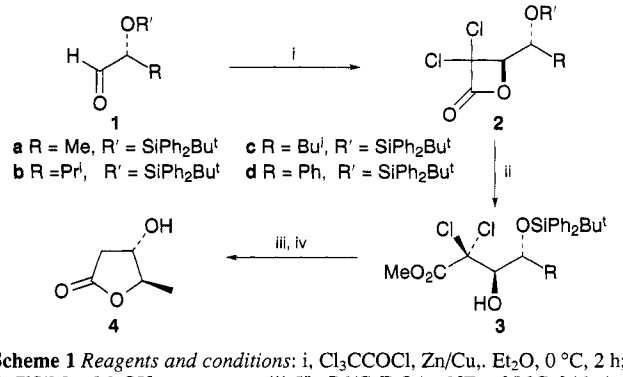
A new route to natural products containing 1,2-diol and 1,2-amino alcohol subunits based on the [2 + 2] cycloaddition of dichloroketene to α-oxyaldehydes and α-amino aldehydes is demonstrated.

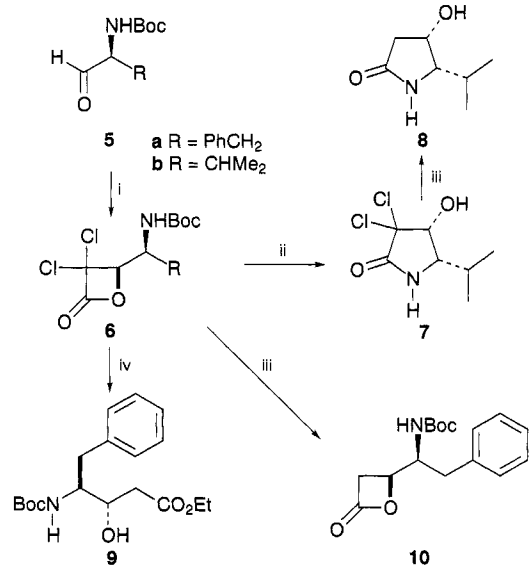
The cycloaddition of ketenes, particularly halogenated ketenes,[1] with carbonyl compounds is a powerful approach to β-lactones.[2] These small ring systems are of particular significance both because of their intrinsic reactivity, which has been utilized in the synthesis of more complex organic compounds,[2] polymers[3] and amino acids,[4] and because of their occurrence in nature.[5] However, despite this no satisfactory asymmetric induction in ketene–aldehyde cycloadditions has been achieved to date.[6] The only reported investigations on this topic dealt with the use of chiral Lewis acids as activators for the reaction,[7] and unfortunately the enantioselectivities for these systems were not high. On the other hand, there is considerable interest in reactions of α-oxyaldehydes[8] and α-amino aldehydes[9] as a means by which 1,2-diol and 1,2-amino alcohol functionalities can be constructed with high stereoselectivity. However, despite its great synthetic potential the [2 + 2] cycloaddition between ketenes and these aldehydes has remained unexplored in comparison to the [4 + 2] cycloaddition which has been investigated intensively.[10]

The first aim of our investigation was, therefore, to provide insight into the chemical and stereochemical behaviour of α-oxyaldehydes **1**, as representative substrates, in [2 + 2] cycloadditions. For example, slow addition of trichloroacetyl chloride to a mixture of the *O*-*tert*-butyldiphenylsilyllactaldehyde **1a** and Zn/Cu[11] in diethyl ether afforded after aqueous workup an oil which on purification by silica gel flash chromatography led to the β-lactone **2a** in 85% yield (Scheme 1). Examination of the crude product by ^{1}H NMR (300 MHz) indicated that only one diastereoisomer had been formed. Next, α-silyloxyaldehydes **1b**, **1c** and **1d** were subjected to cycloaddition with dichloroketene under the same conditions as above. In every case, a single diastereoisomer was detected in the ^{1}H NMR spectra of the respective crude products, and the chemical yields were uniformly good after purification by column chromatography.† To establish the stereochemical course of these cycloadditions, the β-lactone **2a** was transformed into the known γ-lactone **4**.[12] Treatment of **2a** with trimethylchlorosilane in methanol afforded the methyl ester **3** {$[\alpha]_D^{25}$ = −16.8 (*c* = 1.54, CH_2Cl_2)}, which on treatment with H_2 and 10% Pd/C in the presence of triethylamine gave the corresponding β-hydroxy-γ-silyloxy ester. *O*-Silyl deprotection accompanied by spontaneous lactonization gave the γ-lactone **4**, obtained in 76% overall yield, which showed spectral data consistent with the known compound **4** {$[\alpha]_D^{25}$ = +10.8 (*c* = 1.25, $CHCl_3$); Lit.[12] $[\alpha]_D^{25}$ = +10.9 (*c* = 1.27, $CHCl_3$)}, thus confirming the assigned stereochemistry for the adducts.



Scheme 1 *Reagents and conditions*: i, Cl_3CCOCl, Zn/Cu,. Et_2O, 0 °C, 2 h; ii, $ClSiMe_3$, MeOH, room temp.; iii, H_2, Pd/C, EtOAc, NEt_3, 25 °C, 24 h; iv, Bu_4NF, CH_2Cl_2, room temp.

In view of the above results, we next examined the reaction of dichloroketene with the *N*-Boc-α-amino-aldehydes **5a** and **5b** to establish the potential scope of the methodology (Scheme 2). For instance, the reaction of dichloroacetyl chloride and triethylamine with **5a** in dichloromethane at −78 °C to room temp. overnight afforded an oil which on purification by silica gel flash chromatography led to the crystalline β-lactone **6a** in 44% yield {mp 124–125 °C, $[\alpha]_D^{25}$ = +32.3 (*c* = 1.0, CH_2Cl_2)}. The ^{1}H NMR (300 MHz) spectrum of the crude product indicated the exclusive formation of one diastereoisomer. As in the earlier cases, this cycloadduct could also be transformed into the γ-lactam **7a** {85%, mp 119–120 °C, $[\alpha]_D^{25}$ = −17.2 (*c* = 0.8, EtOH)} by simple treatment of **6a** with $ClSiMe_3$ in methanol. In a similar way, reaction of dichloroketene, generated from trichloroacetyl chloride and Zn/Cu, with **5b** followed by intramolecular cyclization as above afforded the γ-lactam **7b** in 35% overall yield {mp 186–187 °C, $[\alpha]_D^{25}$ = −30.8 (*c* = 0.6, EtOH)}. The absolute stereochemistry of the products was unambiguously determined either by conversion of **7b** into the known compound **8**,[13] or by the synthesis of (3*S*,4*S*)-4-amino-3-hydroxy-5-phenyl pentanoic acid ethyl ester **9**,[14] the key component of the HIV protease inhibitor AHPPA.[15] The latter was easily accomplished by simple exposure of **6a** to hydrogenolysis in EtOH for 20 h to furnish **9** in 81% isolated yield.‡ When dehalogenation of **6a** was conducted under non-solvolytic conditions the β-lactone ring was preserved intact giving **10** {mp 114–116 °C, $[\alpha]_D^{25}$ = −9.4 (*c* = 0.56, CH_2Cl_2)} as a white crystalline compound in almost quantitative yield.



Scheme 2 *Reagents and conditions*: i, $Cl_2CHCOCl$ (4 equiv.), NEt_3 (8 equiv.), CH_2Cl_2, −78 °C → 25 °C, 6 h or Cl_3CCOCl, Zn/Cu, Et_2O, 0 °C, 2 h; ii, $ClSiMe_3$, MeOH, 25 °C, 6 h; iii, H_2, Pd/C, NEt_3, EtOAc, 25 °C; iv, H_2, Pd/C, NEt_3, EtOH, 25 °C, 24 h

In summary, we have demonstrated for the first time that 1,2-diol and 1,2-amino alcohol subunits can be constructed with predictable stereochemistry *via* [2 + 2] cycloadditions between dichloroketene and both α-oxyaldehydes and α-amino aldehydes.§ Consequently, a new methodology for creation of 1,2-difunctionality is provided[16] which should be readily applicable to diverse targets of biological and pharmacological interest.

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Footnotes

† All β-lactone poducts were stable under chromatographic purification. The only exception was **2d** which was directly transformed into **3d**. Structure and configuration of the compounds prepared have been confirmed by spectroscopic data (IR, NMR and MS). **2a**: 85%, $[\alpha]_D^{25}$ = +26.2 (*c* = 1.0, CH_2Cl_2); **2b**: 65%, $[\alpha]_D^{25}$ = +21.1 (*c* = 1.0, CH_2Cl_2); **2c**: 55%, $[\alpha]_D^{25}$ = +17.7 (*c* = 1.0, CH_2Cl_2).

‡ The γ-lactam **8** {mp 128–129 °C, $[\alpha]_D^{25}$ = −12.2 (*c* = 1.0, CH_2Cl_2); Lit.[13] $[\alpha]_D^{25}$ = −12.0 (*c* = 0.45, CH_2Cl_2)} and the β-hydroxy ester **9** {mp 86.88 °C, $[\alpha]_D^{25}$ = −32.5 (*c* = 0.8, MeOH); Lit.[14] $[\alpha]_D^{26}$ = −36.9 (*c* = 1.0, MeOH)} were transformed into the corresponding Mosher esters to prove their enantiomeric purity. In both cases a single set of signals in their respective ^1H and ^{19}F NMR spectra were detected.

§ Although the precise knowledge of the origin of asymmetric induction requires further study, analysis of the Cram's rule formulation *via* the Felkin–Anh model may account for the results obtained with α-oxyaldehydes whilst in the case of α-amino aldehydes the stereoselectivity observed can be attributed to the prior formation of a five-membered chelate and/or an assisted hydrogen bonding model between the 2-amino group and the carbonyl oxygen function. For a recent review on Cram's rule formulation see: J. Mulzer in ref. 8(*c*), p. 3.

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