Pergamon

Tetrahedron Letters, Vol. 36, No. 24, pp. 4159-4162, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00716-4

Highly Diastereoselective [2+2] Cycloadditions via Chelation Control: Asymmetric Synthesis of β-Lactones

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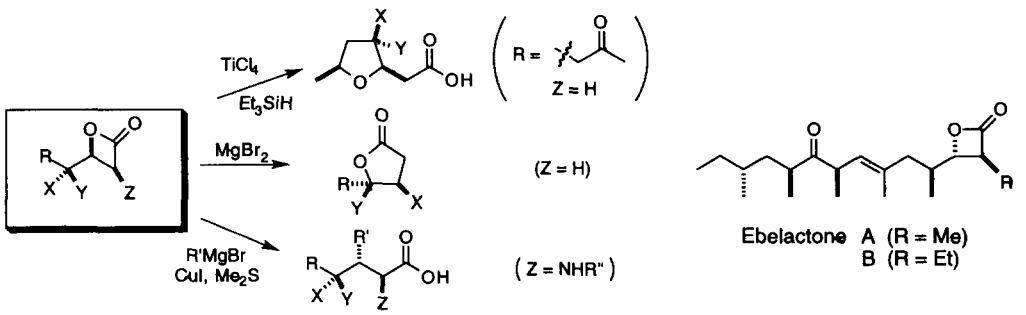
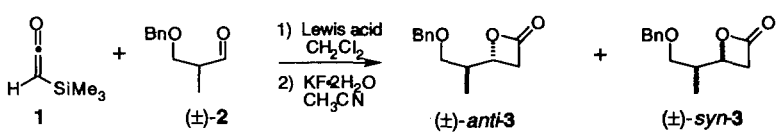
Abstract: Chelation controlled [2+2] cycloadditions of trimethylsilylketene to chiral α- and β-benzyloxyaldehydes followed by desilylation provides a highly diastereoselective route to functionalized β-lactones. Several Lewis acids were examined and $MgBr_2 \cdot Et_2O$ was found to give the highest diastereoselectivities and yields.

β-Lactones are useful intermediates in the synthesis of a variety of more complex molecules including tetrahydrofurans, tetrahydropyrans, γ-lactones, and unnatural amino acids.[1] In addition, several natural products containing β-lactones possess potent biological activity. For example, ebelactones A and B are potent lipase inhibitors.[2]



In connection with a natural product synthesis, we required an asymmetric route to *anti*-β-lactone **3**. We were attracted to the possibility of a chelation controlled [2+2] cycloaddition[3] of trimethylsilyl ketene **1**[4] to the alkoxy aldehyde **2**[5] with chelating Lewis acids.[6] To our knowledge, a chelation controlled strategy has not been employed for [2+2] cycloadditions of ketenes to aldehydes.[7] In this letter we report that highly diastereoselective, chelation-controlled [2+2] cycloadditions can be achieved with aldehydes bearing α- or β-benzyloxy groups allowing access to stereochemically defined β-lactones (*eg.* **3**).



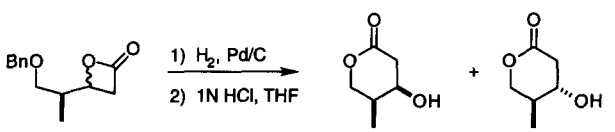
Several Lewis acids were studied for their ability to direct and promote the [2+2] cycloadditions (Table I). Intermediate α-trimethylsilyl β-lactones in this sequence were not isolated, but instead were directly desilylated with potassium fluoride dihydrate[6c] to provide β-lactones **3**. As has been previously observed,[6] use of BF_3•Et_2O led to low diastereoselectivity (entry 1). Better results were obtained with bidentate Lewis acids such as $TiCl_4$ and $SnCl_4$ but several uncharacterized byproducts were also obtained resulting in low overall yields (entries 2 and 3). In contrast, $MgBr_2$•Et_2O gave high diastereoselectivity and overall yield for the two step sequence. Raising the reaction temperature slightly lowered the yield but did not significantly alter the diastereomeric ratio (entry 5 vs 4).

Table I. Diastereoselectivity of [2+2] Cycloadditions of Ketene **1** and Aldehyde (±)-**2** as a Function of Lewis acid and Temperature.

entry	Lewis acid	temp. (°C)	*anti*/*syn* ratio (**3**)[a]	% yield[b]
1	BF_3•OEt_2	0	1.8 : 1	83
2	$TiCl_4$	-78	95 : 5	36
3	$SnCl_4$	-78	97 : 3	76
4	$MgBr_2$•OEt_2	-43	98 : 2	94
5	$MgBr_2$•OEt_2	-23	97 : 3	87

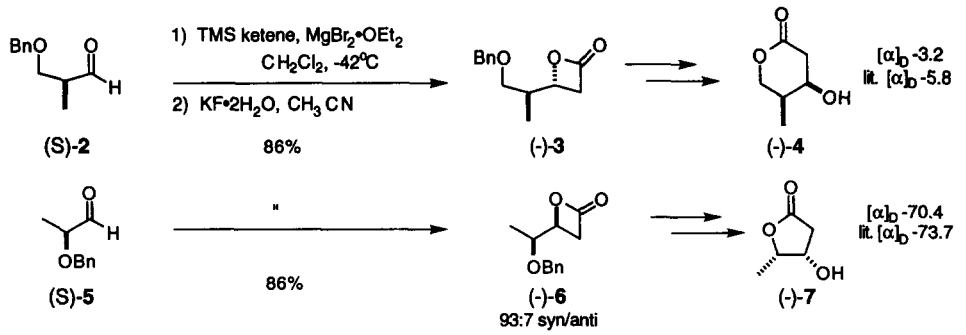
[a] Diastereomeric ratios were determined by ^{1}H-NMR (200 MHz) in C_6D_6 by integration of the benzylic hydrogens. [b]Yields refer to the purified (silica gel chromatography) products as mixtures of diastereomers for the two steps.

The stereochemical outcome of the cycloaddition was determined by conversion of β-lactone **3** to the known δ-lactone **4**.[8] Spectral comparisons indicated that the major β-lactone obtained with all Lewis acids studied possessed the *anti* configuration (*i.e.* *anti*-**3** → *syn*-**4**).

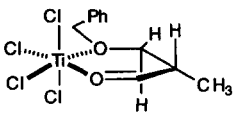


(±)-**3** (±)-*syn*-**4** (±)-*anti*-**4**

Optically pure aldehydes (S)-**2** and (S)-**5**[9] were also examined to determine if absolute stereochemical integrity was maintained in these cyloadditions. The derived β-lactones (-)-**3** and (-)-**6** were converted to the known δ- and γ-lactones (-)-**4**[8] and (-)-**7**,[10] respectively. Spectral comparison (^{1}H, ^{13}C-NMR) established that the cycloaddition of aldehyde (S)-**5** had also proceeded with chelation control. Comparison of optical rotations of the derived lactones (-)-**4** and (-)-**7** with values reported in the literature for these compounds, indicated that partial racemization of the starting aldehydes had occurred. For more rigorous enantiomeric purity determination of β-lactone (-)-**3**, Mosher esters[11] of the debenzylated β-lactone (-)-**3**, the δ-lactone (-)-**4**, and the corresponding racemic compounds were prepared. Integration of the resolved methyl doublets (400 MHz ^{1}H-NMR) indicated the presence of ~6% of the enantiomeric β-lactone, corresponding to ~88% ee for the β-lactone (-)-**3**. We are currently seeking the origin of this racemization and methods to prevent it.



In summary, $MgBr_2$•OEt_2 mediated, [2+2] cycloadditions of ketenes to aldehydes bearing α- or β-benzyloxy groups have been found to proceed with high diastereoselectivities. This is in accord with chelation controlled aldol, allylation and cyclocondensation reactions of heteroatom substituted aldehydes.[12] The origin of this selectivity is likely a result of the high facial bias imparted by formation of the conformationally rigid chelates (*cf.* **8**) of α or β-benzyloxy aldehydes with titanium or magnesium Lewis acids.[13] In view of the utility of β-lactones as intermediates in synthesis due to their ability to undergo a variety of ring opening and ring expansion reactions, the present method should prove useful as it facilitates access to optically active, functionalized β-lactones. Novel transformations of these and other β-lactones in addition to applications of the present methodology to natural product synthesis will be the subject of future reports.



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Representative Procedure for Chelation Controlled [2+2] Cycloaddition/Desilylation Sequence: A solution of aldehyde **2** (230 mg, 1.28 mmol) in 2 mL (plus 0.5 ml rinse) of dry CH_2Cl_2 was added via cannula to a slurry of 372 mg (1.41 mmol) $MgBr_2$•OEt_2 in 2 mL of CH_2Cl_2 at -42 °C (CH_3CN/CO_2 or Cryocool) under nitrogen. After 15 min a solution of trimethylsilylketene (196 mL, 1.41 mmol) in 2 mL of CH_2Cl_2 was added via syringe pump over 15 min. The reaction mixture was stirred at -42 °C under nitrogen for 7 h and then quenched at that temperature by addition of 1 mL water. After warming to ambient temperature the organic layer was separated, the aqueous phase was extracted with CH_2Cl_2 (3x2 mL) and the combined organics were filtered, dried over Na_2SO_4 and evaporated *in vacuo*. The resulting colorless oil was dissolved in 3 mL CH_3CN and solid KF•$2H_2O$ (180 mg, 1.92 mmol) was added. The mixture was stirred at ambient temperature for 30 min, passed through a short column of florisil and evaporated *in vacuo*. Purification by flash column chromatography (gradient elution: 10%→25% ethyl acetate/hexane by 5% increments) provided 239 mg (86%) of β-lactone (-)-**3** as a colorless oil.[14]

Acknowledgment: Support of these investigations by Texas A&M University and the Robert A. Welch Foundation (A-1280) is gratefully acknowledged. We thank Mr. R. M. Rzasa and Mr. H. W. Yang for acquiring 400 MHz NMR spectra. D.R. thanks colleagues in the Texas A&M Chemistry Department for helpful discussions.

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i ii

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14. Data for β-lactone (-)-**3**: $[\alpha]^{22}_D$ = 11.2 (*c* 1.97, $CHCl_3$), IR(neat) 1127, 1827 cm^{-1} ; ^1H-NMR (C_6D_6, 200 MHz) d 0.57(3H, d, J=6.9 Hz), 1.41-1.61(1H, m), 2.45(1H, dd, J=16.2, 4.6 Hz), 2.58(1H, dd, J=16.2, 5.8 Hz), 3.06-3.21(2H, m), 3.78-3.90 (1H, m), 4.19 (2H, app s), 7.10-7.22 (5H, m); ^{13}C-NMR ($CDCl_3$, 50 MHz) d 11.8, 37.8, 41.0, 71.0, 72.2, 73.5, 127.6, 128.4, 138.3, 167.8; MS m/z (relative intensity) 221 (M^+, 100), 154 (92), 137 (96); FAB HRMS calcd. for $C_{13}H_{16}O_3$ (M^++H): 221.1177, found: 221.1193. β-Lactone (-)-**6** also exhibited spectral characteristics in accord with its structure.

(*Received in USA* 29 *March* 1995; *accepted* 13 *April* 1995)