Enantioselective Synthesis of Alkyl-substituted Eight-membered Lactones by Claisen Rearrangement

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Abstract: The Claisen rearrangement of alkenyl-substituted ketene acetals (produced in situ by selenoxide elimination from the corresponding phenylselenoacetaldehyde-derived acetals of enantiomerically pure 1,3-diol derivatives) afforded unsaturated eight-membered lactones with control of stereochemistry of methyl substituents at C-4, C-5 and C-7, as well as a fused system.

Key words: [3.3]-sigmatropic, lactone, aldol, boron, enantioselective

Recent efforts in this laboratory have focused on the synthesis of unsaturated medium ring heterocycles (lactones and lactams) by the Claisen rearrangement involving a two-atom ring expansion[1] of a vinyl-substituted ketene acetal[2-6] (or aminal).[7] Owing to the normal preference for a chair-like transition state and the constraint of a *Z*-double bond in the medium ring product (Fig. 1; R^2 = H) enantiomerically pure disubstituted lactones could be obtained from the corresponding 1,3-diol precursors.[5] Other approaches to unsaturated lactones have been reviewed in detail.[8-10] Among these lactonizations of seco-acids containing a (*Z*)-alkene have been employed.[6,11] Even a saturated seco-acid containing a (presumably) pre-ordered conformation has been lactonized efficiently.[11] Here we report that the Claisen ring expansion can be applied to trisubstituted alkene precursors in the efficient preparation of unsaturated eight-membered lactones with up to three substituents in four different positions.

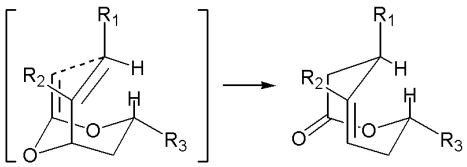
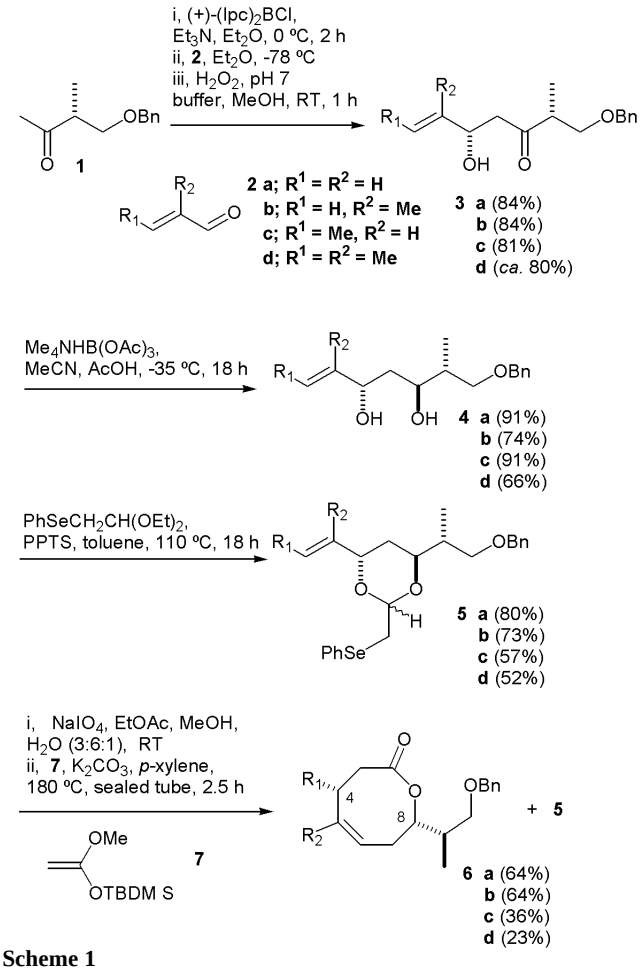


Figure 1 Chair-like transition state for the Claisen rearrangement of vinyl-substituted ketene acetals derived from1,3-diols.

An Ipc-boron mediated aldol reaction[12-14] of the enolate derived from the ketone **1**[8,11] and the commercially available aldehydes **2a-d** provided the 1,4-*syn* products **3** in 81-84% yields as single diastereoisomers as judged by NMR (Scheme 1). (*R*)-(+)- and (*S*)-(-)-Phenylmethoxy(trifluoromethyl) acetate derivatives of the product **3a** were prepared, and the absolute configuration of the secondary alcohol centre was assigned by 500 MHz ^{1}H NMR analysis following the method of Kakisawa.[18] Careful chromatographic purification provided the pure β-hydroxyketones **3a-c**, but compound **3d** could not easily be separated from isopinocampheol (arising from the oxidative work-up of the intermediate borates), and it was used in the crude form.

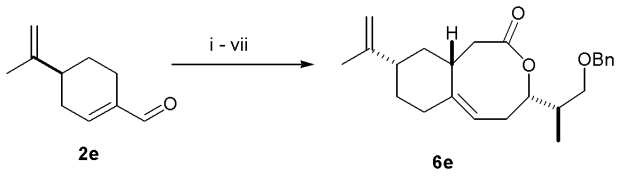
The β-hydroxyketones **3** were then treated with $Me_4NHB(OAc)_3$ to provide the *anti* diols **4** in good yield.[19] At -35 °C the reduction was complete in 18 h to afford a single diastereoisomer as judged by ^{1}H NMR. However, at -30 °C, reduction of the keto-alcohol **3b** afforded a diastereoisomeric mixture.



Scheme 1

The diols **4** were converted with phenylselenoacetaldehyde diethyl acetal[1] in the presence of pyridine 4-toluenesulfonate (PPTS) in refluxing toluene into the phenylseleno acetals **5** which were purified by chromatography. The reaction was slow and required a stoichiometric quantity of PPTS for complete reaction.

Oxidation of the selenides **5** was achieved with sodium metaperiodate; the resulting selenoxides were used without chromatographic purification.[2-7] Selenoxide elimination in refluxing xylene at 180 °C (sealed tube) in the presence of K_2CO_3 and the ketene acetal **7**[5,7,20] afforded the 8-membered unsaturated lactones **6** together with significant amounts of the starting selenides **5** (6-49%) which were thought to be produced by disproportionation reactions.[21] Good yields were obtained when the substrate did not contain a terminal methyl substituent (see **5a, 5b**). The relative stereochemistry of the substituted lactones **6c** and **6d**, assigned on the basis of ^{1}H NMR NOE enhancements observed between H-4 and H-8, is in accord with that predicted from the chair-like transition state depicted in Figure 1.



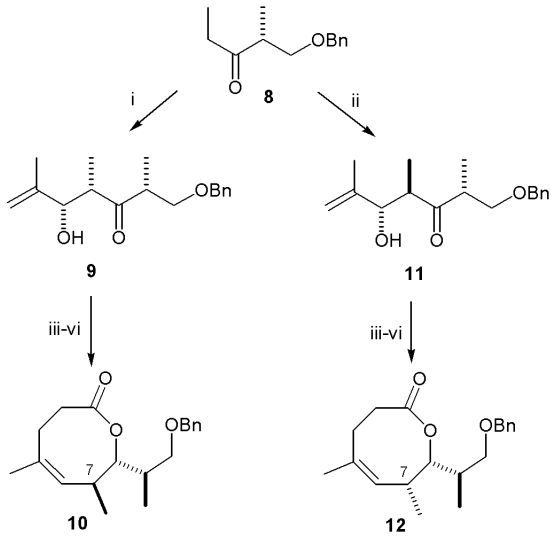
Scheme 2 *Reagents and conditions*: i, **1**, (+)-$(Ipc)_2BCl$, Et_3N, Et_2O, 0 °C, 2 h; ii, **2e**, Et_2O, -78 °C 1.5 h; iii, H_2O_2, pH 7 buffer, MeOH, 25 °C, 1 h; iv, $Me_4NHB(OAc)_3$, MeCN, AcOH, -35 °C, 18 h (51%, 2 steps); v, $PhSeCH_2CH(OEt)_2$, PPTS, DME, 85 °C, 18 h (67%); vi, $NaIO_4$, EtOAc, MeOH, H_2O (3:6:1), 25 °C ; vii, **7**, DBU, *m*-xylene, 180 °C, sealed tube, 5 h, (55%, 2 steps).

It was found that the use of DBU instead of K_2CO_3 as base in the elimination of the selenoxide from **5a** increased the yield of **6a** to 71%, probably owing to the improved solubility of the base in xylene. Carrying the reaction out at 138 °C in refluxing xylene reduced the yield to 61%. The yield of **6d** was improved to 33% by use of DBU and a longer reaction time.

Fused bicyclic systems can also be prepared. Thus the commercially available (-)-perilaldehyde **2e** was converted into the bicyclic lactone **6e** in 19% yield over 5 steps (Scheme 2). Although the double bond in the Claisen precursor is terminally substituted the yield of the Claisen rearrangement (55%) was higher than those recorded for precursors carrying terminal methyl substituents (**6c,d**).

Use of the ethyl analogue **8** of the methyl ketone **1** in the aldol reaction with methacrolein in the presence of the Ipc- (*syn*-aldol) and dicyclohexyl boron ligands (*anti*-aldol) gave respectively the β-hydroxyketones **9** and **11**.[14] These products were then converted into the corresponding lactones with a stereodefined methyl substituent at C-7 (Scheme 3).

In summary, a Claisen ring expansion method for the synthesis of substituted eight-membered lactones is described.[22] Furthermore, when combined with the powerful stereochemical control available from the Paterson boron-mediated aldol reactions[12-14] and the Evans reduction of β-hydroxy ketones to *anti*-1,3-diols,[19] the method lends itself to the construction of lactones such as the octalactins[11] and unusual alkene substitution patterns as may occur in polyketide antibiotics such as discodermolide.[23] The latter would be farmore difficult to realise by acyclic versions of the Claisen rearrangement.



Scheme 3 *Reagents and conditions*: i, **8**, (-)-$(Ipc)_2BOTf$, $^iPr_2NEt$,CH_2Cl_2, 25 °C, 3 h; methacrolein, -5 °C, 18 h; H_2O_2, pH 7 buffer, MeOH, 25 °C, 1 h (90 %); ii, **8**, $(Chx)_2BCl$, Et_3N, Et_2O, -78 °C, 3 h; methacrolein,-78 °C, 18 h; H_2O_2, pH 7 buffer, MeOH, RT, 1 h (72 %); iii, $Me_4NHB(OAc)_3$, MeCN, AcOH, -35 °C, 18 h (56-72%); iv, $PhSeCH_2CH(OEt)_2$, PPTS, toluene, 110 °C, 18 h (96-99%); v, $NaIO_4$, EtOAc, MeOH, H_2O (3:6:1), 25 °C; vi, **7**, DBU, *m*-xylene, 180 °C, sealed tube, 2.5-5 h (61-95%).

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References and Notes

(1) Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 3075.
(2) Carling, R. W.; Holmes, A. B. *J. Chem. Soc., Chem. Commun.* **1986**, 565.
(3) Curtis, N. R.; Holmes, A. B.; Looney, M. G. *Tetrahedron* **1991**, *47*, 7171.
(4) Congreve, M. S.; Holmes, A. B.; Hughes, A. B.; Looney, M. G. *J. Am. Chem. Soc.* **1993**, *115*, 5815.
(5) Fuhry, M. A. M.; Holmes, A. B.; Marshall, D. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2743.

(6) Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J.G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483.
(7) Evans, P. A.; Holmes, A. B.; McGeary, R. P.; Nadin, A.; Russell, K.; O'Hanlon, P. J.; Pearson, N. D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 123.
(8) Moody, C. J.; Davies, M. J. In *Studies in Natural Product Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science: 1992; Vol. 10; pp201-239.
(9) Elliott, M. C. *Contemp. Org. Synth.* **1994**, *1*, 457.
(10) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777.
(11) Buszek, K. R.; Sato, N.; Jeong, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5511.
(12) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121.
(13) Bernardi, A.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron: Asymmetry* **1995**, *6*, 2613.
(14) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287.
(15) Prepared in three steps from commercially available (*R*)-(+)-methyl-3-hydroxy-2-methylpropionate following the published procedure,[12] but using the method of Williams *et al.*[16] for the preparation of the Weinreb amide as first reported by Paterson and McLeod.[17]
(16) Williams, J. M.; Jobson, R.B.; Yasuda, N.; Marchesini, G.; Dolling, U. H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.
(17) Paterson, I.; McLeod, M. D. *Tetrahedron Lett.* **1997**, *38*, 4183.
(18) Ohtani, I.; Kusumi, T.;Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
(19) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
(20) Danishefsky, S.; Vaughan, K.; Gadwood, R.; Tsuzuki, K. *J. Am. Chem. Soc.* **1981**, *103*, 4136.
(21) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon Press: Oxford, 1987, p. 34 and pp. 136-137.
(22) *Representative procedure for the Claisen rearrangement.* A mixture of the acetal **5b** (0.342 mmol), $NaIO_4$ (2.1 mmol) and $NaHCO_3$ (2.9 mmol) in EtOAc-MeOH-water (3:6:1) was stirred vigorously at ambient temperature for 100 min. The reaction mixture was poured into water (40 ml) and extracted with EtOAc (3 x 100 ml). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated to afford an approximately quantitative yield of the corresponding selenoxide. A solution of the selenoxide and 1-*t*-butyldimethylsiloxy-1-methoxy ethene **7**[16] (5 mmol) in dry *p*-xylene (16.5 ml) with K_2CO_3 (1.9 mmol) was heated under a nitrogen atmosphere in a sealed tube at 180 °C for 2.5 h. The organic phase was removed in vacuo, and the residue was subjected to flash chromatography on silica gel (15% ether-light petroleum 60-80) to yield a mixture of the selenide **5b** (0.091 mmol, 27%) and the lactone **6b** (0.22 mmol, 64%). R_f (15% ether-light petroleum 60-80) 0.23; $[\alpha]_D^{21}$ –13.8 (*c* 0.3 in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.21-7.35(5H, m), 5.44 (1H, t *J* = 8 Hz), 4.45-4.55 (1H, m), 4.50 (2H, s), 3.58 (1H, dd, *J* = 9, 5 Hz), 3.36 (1H, dd, *J* = 9, 7 Hz), 2.11 (1H, dt, *J* = 12, 6 Hz), 2.71 (1H, ddd, *J* = 13, 6, 3 Hz), 2.50-2.46 (2H, m), 2.01-2.12 (2H, m) 1.94 (1H, ddd, *J* = 12, 5, 3 Hz), 1.72 (3H, s) and 1.04 (3H, d, *J* = 7 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 176.8, 140.3, 138.6,128.3, 127.6, 127.5, 122.3, 81.9, 73.2, 72.2, 37.9, 36.6, 32.2, 29.0, 24.2 and 14.2; IR ($CDCl_3$) 1735, 1454, 1219 and 1074 cm^{-1}; *m/z* (CI, rel intensity) 306 [100, $(M + NH4)^+$], 289 [70, (MH)], 181 (25), and 85 (45); *m/z* 289.1804 (289.1804 calcd for $C_{18}H_{25}O_3$, MH).
All other compounds described here showed spectroscopic and analytical data in accord with the assigned structure.
(23) Gunasekera, S. P.; Gunasekera, M.; Longley, R. E. *J. Org.Chem.* **1990**, *55*, 4912. *Ibid* **1991**, *56*, 1346.

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