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Asymmetric Synthesis of α-Keto β-Lactams via [2+2] Cycloaddition Reaction: A Concise Approach to Optically Active α-Hydroxy β-Lactams and β-Alkyl(Aryl)isoserines.

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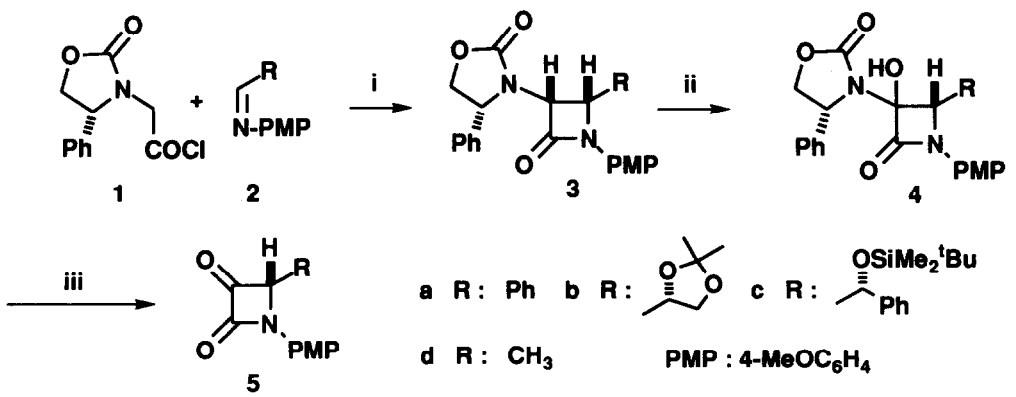
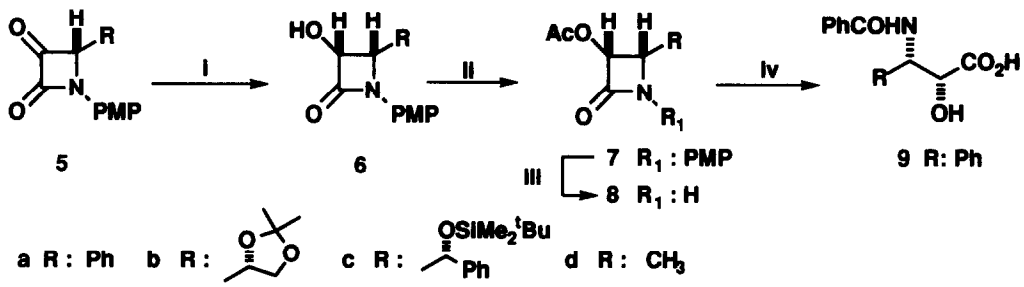
Abstract: The cycloaddition reaction of the Evans-Sjögren ketenes to imines, followed by α-hydroxylation of the resulting cycloadducts provides an efficient general asymmetric synthesis of α-keto β-lactams and derivatives.

The development of asymmetric syntheses of β-lactams is of importance, not only within the context of β-lactam antibiotics, but also in methodology utilizing β-lactams as chiral templates[2]. While abundant information on diverse substitution patterns of optically active β-lactams exists[3], very little is known about the synthesis[4] and applications of monocyclic azetidine-2,3-diones[5] and even less on their optically active derivatives[6]. We report here the first asymmetric synthesis of this class of compounds that illustrates new perspectives in the field of β-lactam chemistry. Thus, reaction of the Evans-Sjögren ketenes[7] (Scheme 1) with either achiral imines or chiral imines followed by α-hydroxylation[8] of the resulting cycloadducts leads to the formation of optically pure α-keto β-lactams with concomitant recovery of the chiral auxiliary.



Scheme 1. Reagents and Conditions: i, NEt_3, CH_2Cl_2, -78°C→r.t., 20-24h; ii $LiN(SiMe_3)_2$ (2 equiv.), THF, -78°C, 1.5h then, MoOPH (3 equiv.), -78°C, 6h iii SiO_2, CH_2Cl_2, r.t., 20-24h.

The starting acid chloride **1** was prepared and reacted with imines **2a-c** under known conditions[7b] to form β-lactams **3a-c** in high yields and with virtually complete diastereoselectivity. When **3a** [83% yield, mp: 240-242°C $[\alpha]_D^{25}$= -91.0 (c= 1.0, CH_2Cl_2)] was deprotonated[9] using lithium bis(trimethylsilyl)amide in THF at -78°C followed by hydroxylation with Vedjes' molybdenum peroxide reagent MoOPH[10] a mixture of the desired α-keto β-lactam **5a** [50%, isolated yield, m.p.: 139-140°C] and the corresponding α-amido carbinol **4a**[11] was produced together with the oxazolidinone chiral auxiliary after column chromatography. This result suggested the expected α-amido carbinols to be relatively unstable and easy to transform into α-keto β-lactams under mild acidic conditions. In fact, exposure of **4a** to silica gel or simple heating in THF gave complete conversion into **5a**. In subsequent experiments carried out without isolation of the corresponding intermediates, β-lactams **3a**, **3b** and **3c** furnished the desired α-keto β-lactams **5a**, **5b** and **5c** in yields ranging from 65-80% (not fully optimized). For instance, **3b** gave the β-lactam **5b** in 65% yield [mp: 143-145°C $[\alpha]_D^{25}$= +38.0° (c= 1.0, CH_2Cl_2)] and **3c**, under the same conditions, led to **5c** in 72% yield [mp: 103-104°C $[\alpha]_D^{25}$= -72.0 (c= 1.0, CH_2Cl_2)]. In a similar way **3d**, prepared from **3b** by a routine elaboration of the C_4 substituent, gave **5d** in 68% yield [m.p. 103-104°C, $[\alpha]_D^{25}$= -72.0° (c= 1.0, CH_2Cl_2)]. The absolute stereochemistry of the cycloadducts as well as the α-keto β-lactams thus obtained, was preliminarily assigned on the basis of the known stereochemical outcome of the cycloaddition reaction, but a rigorous proof of the assigned stereochemistry was provided by the synthesis of the β-lactam **8a**, which is a precursor of the (2S,3R)-3-phenylisoserine **9**, the side chain of the potent antitumor agent taxol[12].



Scheme 2. Reagents and Conditions: i, $NaBH_4$, MeOH, 0°C, ii CH_3COCl, NEt_3, CH_2Cl_2, 0°C→ r.t. iii $(NH_4)_2Ce(NO_3)_6$, CH_3CN-H_2O, 0°C, iv ref. 12

The stereochemistry of **5b** and **5c** was established by an independent route which consisted of the cycloaddition reaction of benzyloxyketene to imines **2b** and **2c** respectively, followed by hydrogenolysis of the corresponding cycloadducts[13]. The resulting β-lactams **6b** [m.p: 199-201°C, $[\alpha]_D^{25}$= +99.9° (c=

0.5, MeOH)] and **6c** [m.p: 148-149°C, $[\alpha]_D^{25}$= -37.5° (c= 1.06, CH_2Cl_2)] were identical to that obtained by sodium borohydride reduction of **5b** and **5c** respectively. In a similar way, **5d** furnished **6d** [m.p: 146-147°C $[\alpha]_D^{25}$= +99.2° (c= 1.0, CH_2Cl_2)] in nearly quantitative yield. In every case the reduction of the carbonyl group proceeded with virtually complete stereoselectivity, thus allowing a new asymmetric synthesis of α-hydroxy β-lactams and derivatives in a concise and straightforward fashion[14]. For instance, **6a** obtained by reduction of **5a** upon exposure to acetyl chloride and triethylamine gave the β-lactam **7** which was directly transformed into **8a** (m.p.: 152-153°C) in 70% yield.

From the above results it seems to be clear that a wide variety of β-lactam precursors of β-amino α-hydroxyacids should be efficiently prepared via the present methodology. Finally, precedent from this laboratory[15] would indicate that the α-keto β-lactams obtained via this approach should also be valuable precursors of α-aminoacid N-carboxyanhydrides and, therefore, α-amino acids and peptides containing them. These aspects are now underway in our laboratory and the results will be forthcoming.

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