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A NOVEL ASYMMETRIC SYNTHESIS OF *CIS*-3-HYDROXY-4-ARYL AZETIDIN-2-ONES

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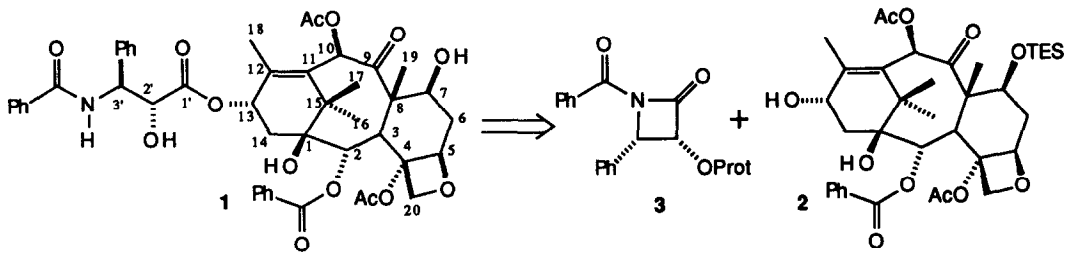
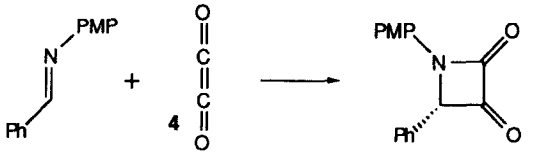
Abstract: Optically pure 3-keto-4-aryl azetidin-2-ones were prepared in high yield via the Staudinger reaction of an oxazolidone substituted ketene. Subsequent reduction with sodium borohydride quantitatively provided chiral *cis*-3-hydroxy-4-aryl azetidin-2-ones.

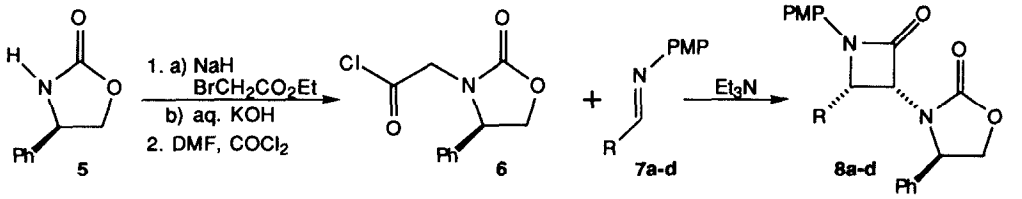
The diterpene taxol (**1**), isolated from the bark of the Pacific yew (*Taxus brevifolia*),[1] has, because of its exciting *in vivo* antitumor activity,[2] its unique mechanism of action,[3] and its taxane carbon skeleton bearing a dense array of functionality, received extraordinary attention from both the biological and chemical communities.[4] The shortage of taxol has, in the past, delayed clinical trials and threatened the survival of the Pacific yew and its primary habitat, the virgin rainforest of the Pacific northwest.[5] Now, the industrialization of an efficient semisynthesis[6] of taxol from 7-O-triethylsilyl baccatin III[7] (**2**) and a suitably protected β-lactam (e.g., **3**) promises to alleviate this shortage. Although the esterification of **2** proceeds with high diastereoselectivity in many cases, there is still an occasional need for β-lactams of high optical purity, and several procedures for obtaining them have been reported.[8]



The ketene-imine cycloaddition process (the Staudinger reaction)[9] is known to provide simple and direct access to the β-lactam nucleus. When carried out with E imines and monosubstituted ketenes, this reaction usually affords *cis* disubstituted β-lactams with high stereoselectivity. Here we report the synthesis of chiral α-keto-β-lactams by the Staudinger reaction[10] and their conversion into the corresponding chiral *cis*-3-hydroxy-4-phenyl azetidin-2-ones. Conceptually, ketene **4** is the reagent required to prepare α-keto-β-lactams. However, ketene **4** is only a compound of theoretical interest and has so far defied experimental detection.[11]



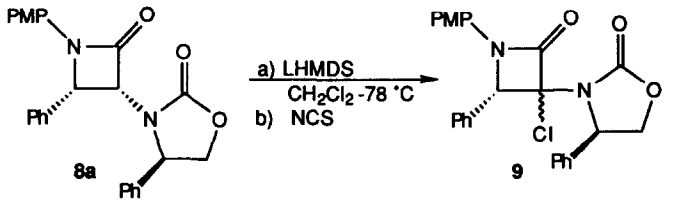
Taking advantage of the fact that chiral *cis*-β-lactam can be obtained with high diastereoselectivity from the Staudinger reaction utilizing a chiral oxazolidone substituted ketene,[12] several chiral *cis*-β-lactams with 3*R*, 4*S* absolute stereochemistry were prepared. Alkylation of oxazolidone **5** with ethyl bromoacetate afforded the ethyl ester which underwent *in situ* saponification, and the acid was then converted (oxalyl chloride) to acid chloride **6** in 94% overall yield. The acid chloride was converted to the ketene (Et_3N, -78 °C) which then reacted with imines **7a-d** to give chiral *cis*-β-lactams **8a-d**[13] in high yield with complete diastereoselectivity.



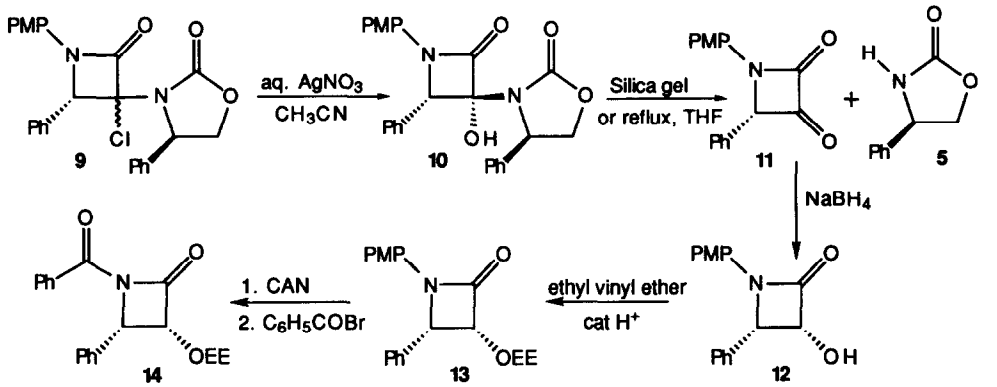
β-Lactam	Imine (R)	Yield	$[\alpha]_{Hg}^{25}$ (concentration, $CHCl_3$)
8a	**7a** (phenyl)	93%	-137.5° (1.63)
8b	**7b** (4-methoxyphenyl)	83%	-132.2° (1.54)
8c	**7c** (2-furyl)	95%	-98.5° (1.73)
8d	**7d** (cinnamyl)	86%	-119.5° (1.58)

Halogenation of carbon-3 in β-lactam **8a** followed by hydrolysis was expected to provide the corresponding chiral α-keto-β-lactam. Attempted halogenation of **8a** under free radical conditions (NBS or SO_2Cl_2) generated complicated mixtures, presumably due to competing benzylic halogenation. During efforts to halogenate the enolate of **8a** a severe solubility problem was encountered. β-Lactam **8a** has low solubility in ethereal solvents (2.5×10^{-3} M in THF at -78 °C, slightly greater in DME, much lower in ether), but it was found to be soluble in dichloromethane. Therefore, a solution of β-lactam **8a** in dichloromethane was added to a solution of lithium hexamethyldisilazide (LHMDS) in THF at -78 °C. After one hour at -78 °C *N*-chlorosuccinimide was added, and, after aqueous workup, a mixture of labile α-chloro-β-lactams **9**, epimeric at carbon-3, was obtained. When the same experiment was conducted in dichloromethane alone, β-lactam **8a** was transformed into a mixture of α-chloro-β-lactams **9** in greater than 95% yield.

To the best of our knowledge, this reaction represents the first example of formation and reaction of a lithium enolate in dichloromethane. This result raises several issues, including the identity of the base in dichloromethane as well as the reactivity of *n*-butyllithium with dichloromethane, and these issues are under active investigation in our laboratory.



The crude mixture of α-chloro-β-lactams **9** was subjected to dechlorination (aq $AgNO_3$, CH_3CN) at 0 °C for 4 h to give only β-lactam **10**. The *trans* stereochemistry of the chiral auxiliary and the phenyl group at carbon-4 was determined by ^1H nOe analysis. β-Lactam **10** was found to undergo decomposition either thermally (anhydrous THF, reflux 3 h) or upon exposure to silica gel (25 °C, 16 h) to provide α-keto-β-lactam **11**[10,13] and recovered oxazolidone **5** quantitatively. The crystalline β-lactam **10** had a decomposition point (141 °-142 °C) which was almost identical to the melting point (140 °-141 °C) of α-keto-β-lactam **11**. The identity of **10**, **11**, and **5** was confirmed by CI mass spectroscopy [hemiaminal **10**: m/e 431.1 $(M+1)^+$, relative abundance 22.3%; α-keto-β-lactam **11**: m/e 268.2 $(M+1)^+$, base peak 100%; oxazolidone **5**: m/e 164.1 $(M+1)^+$, relative abundance 33.3%]. The conversion of **8a** to **11** could most conveniently be carried out without isolation of intermediates in ca. 95% yield.



α-Keto-β-lactam **11** was reduced by sodium borohydride in methanol (0 °C) to afford *cis*-3(*R*)-hydroxy-4(*S*)-phenyl β-lactam **12**[13] in quantitative yield. The optical purity of **12** was determined by ^1H NMR analysis of the corresponding (*S*)-(-)-MTPA ester, and only a single diastereomer could be detected. Protection of **12** (ethyl vinyl ether, cat. CH_3SO_3H, THF, 0 °C, 100%) followed by dearylation (CAN, aq. CH_3CN, -5 °C, 87%) and benzoylation (C_6H_5COBr, pyr, CH_2Cl_2, 0 °C, 98%) provided optically pure β-lactam **14**[13] in eight steps and 71% overall yield from oxazolidone **5**. This procedure constitutes a most efficient asymmetric synthesis of the taxol side chain precursor[6,10] or taxol synthon.[6]

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